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(19)(CA) APPLICATION FOR CANADIAN PATENT (12)

(54) Sulfonamides and Their Medical Use

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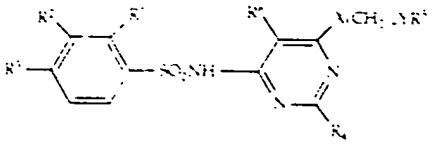
Abstract

Sulphonamides of formula I, in which the symbols R^1-R^5, X, Y and n have the significance given in the description and which are in part novel compounds, and salts thereof can be used as active ingredients for the manufacture of medicaments for the treatment of circulatory disorders, especially hypertension, ischemia, vasospasms and angina pectoris.

RAN 4019/114

The present invention is concerned with the use of sulphonamides as medicaments and with novel sulphonamides. In particular, the invention is concerned with the use of compounds of the formula



I

wherein

R^1 signifies hydrogen, lower-alkyl, lower-alkoxy, lower-alkylthio, halogen or trifluoromethyl;

R^2 signifies hydrogen, halogen, lower-alkoxy, hydroxy-lower-alkoxy or trifluoromethyl; and

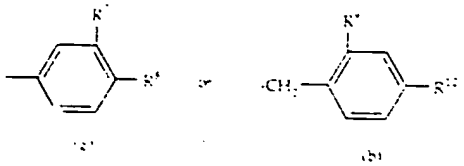
R^3 signifies hydrogen, hydroxy, halogen, alkylthio, cycloalkyl, hydroxy-lower-alkyl, hydroxy-lower-alkoxy, hydroxyimino-lower-alkyl, lower-alkenyl, oxo-lower-alkyl, trifluoromethyl, trifluormethoxy, lower-alkoxy, lower-alkoxy-lower-alkoxy or aryl-lower-alkoxy; or

R^2 and R^3 together signify butadienyl;

R^4 signifies hydrogen, lower-alkyl, aryl or heteroaryl;

R^5 signifies hydrogen, lower-alkanoyl, benzoyl, heterocyclyl-carbonyl or tetrahydropyran-2-yl;

R^6 signifies a residue of the formula



Ia Ib

Grn/10.3.92

R^{7} signifies hydrogen, lower-alkoxy or nitro; and

R^{8} signifies hydrogen, halogen, lower-alkyl, lower-alkoxy, lower-alkylthio, nitro, hydroxy, amino or trifluoromethyl; or

R^{7} and R^{8} together signify butadienyl;

R^{9} signifies hydrogen, halogen, lower-alkyl, lower-alkoxy, lower-alkylthio or trifluoromethyl;

R^{10} signifies hydrogen, halogen, lower-alkyl, lower-alkoxy or lower-alkylthio;

X and Y each independently signify O, S or NH; and

n signifies 2, 3 or 4;

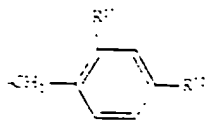
and salts thereof as active ingredients for the manufacture of medicaments for the treatment of circulatory disorders, especially hypertension, ischemia, vasospasms and angina pectoris.

The term "lower" used here denotes groups with 1-7 C atoms, preferably 1-4 C atoms. Alkyl, alkoxy, alkylthio and alkenyl groups as well as alkyl groups as components of alkanoyl groups can be straight-chain or branched. Methyl, ethyl, propyl, isopropyl, butyl, sec. and tert.butyl are examples of such alkyl groups. Vinyl and allyl are examples of alkenyl groups. Aryl-lower-alkoxy is, for example, benzyloxy. Halogen denotes fluorine, chlorine, bromine and iodine, with chlorine being preferred. Examples of aryl residues are phenyl and substituted phenyl residues, with halogen, alkyl and alkoxy especially coming into consideration as substituents. Examples of heteroaryl residues are especially monocyclic 5- and 6-membered heteroaromatic residues having nitrogen or sulphur as the hetero atom, such as pyrimidinyl, pyridyl, pyrazinyl, pyridazinyl and thienyl. Heterocyclyl-carbonyl residues are, e.g., 2-, 3- or 4-pyridylcarbonyl; 3-methylisoxazol-5-yl-carbonyl; 2- or 3-furoyl; and 2- or 3-thenoyl.

Sulphonamides which fall under formula I given above are known from Patent Publication DE 1 545 944. These known sulphonamides have blood pressure lowering activity. It has

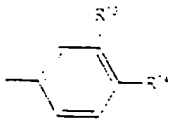
now surprisingly been found that the compounds of formula I given above are inhibitors of endothelin receptors. The compounds of formula I can therefore be used for the treatment of illnesses which are associated with endothelin activities, especially circulatory disorders such as hypertension, ischemia, vasospasms and angina pectoris.

A preferred group of compounds within formula I which are novel compounds comprise those in which R^1 represents a residue of the formula



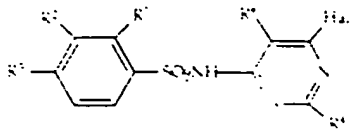
and R^{11} signifies halogen, lower-alkoxy, lower-alkylthio or trifluoromethyl; and R^{12} signifies hydrogen or lower-alkoxy and R^1-R^5, X, Y and n have the significance given above.

A further preferred group of compounds within formula I which are also novel compounds comprise those in which R^1 represents a residue of the formula



and R^{13} signifies hydrogen, lower-alkoxy or nitro; and R^{14} signifies hydrogen, halogen, lower-alkyl, lower-alkoxy, lower-alkylthio or nitro; or R^{13} and R^{14} together signify butadienyl; and R^1-R^5, X, Y and n have the significance given above.

The compounds of formula I can be manufactured by reacting a compound of the formula



wherein R^1, R^2, R^3, R^4 and R^5 have the significance given above and Hal is halogen.

with a compound of the formula

$$MX(CH_2)_nYR^5 \qquad III$$

wherein X, Y, n and R^5 have the significance given above and M is an alkali metal,

and, if desired, modifying substituents present in the resulting compound of formula I and/or converting the compound of formula I obtained into a salt.

In a preferred embodiment of the process a compound of formula II in which R^5 represents a residue (c) or (d) defined above is used as the starting material.

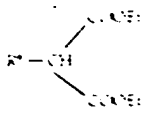
The reaction of a compound of formula II with a compound of formula III is conveniently carried out using the glycol from which the compound III is derived, e.g. ethylene glycol when n = 2. The alkali metal M is preferably sodium. The reaction is conveniently carried out while heating, e.g. to 70-120°C. In a preferred embodiment, the monosodium salt of ethylene glycol, propylene glycol or butylene glycol is used as the compound of formula III.

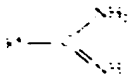
Substituents present in the thus-obtained compound of formula I can be modified. For example, a hydroxy group R^5 can be esterified or etherified. A nitro group can be reduced to the amino group. A lower-alkenyl group R^3 can be oxidized to the carbonyl group or to an alkanone group, e.g. using OsO_4 or $NaIO_4$; the thus-formed carbonyl group can be reduced to the hydroxy group, e.g. using sodium borohydride, or can be converted into a corresponding tertiary alcohol with an alkyl-Grignard compound

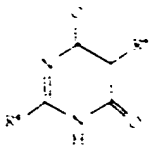
or can be converted into the oxime with hydroxylamine. These conversions can be carried out in a manner known per se, whereby a hydroxy group R^5 is firstly transformed into an ether group, e.g. the tetrahydropyranyl ether, or an ester group, e.g. the acetate. If desired, these groups can again be cleaved off in a manner known per se; alternatively a transformation of a hydroxy group R^5 by esterification or etherification can also be carried out without subsequent transformation of other reactive groups in the molecule. The compounds of formula I can be converted into salts, e.g. alkali salts such as Na and K salts, in a manner known per se.

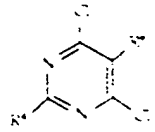
The compounds of formulae II and III which are used as starting materials, insofar as they are not known or their preparation is not described hereinafter, can be prepared in analogy to known methods or to methods described hereinafter.

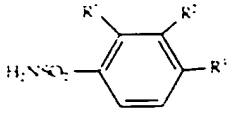
The compounds of formula II can be prepared in accordance with the following Reaction Scheme











Condensation of compound IV with formamidine acetate or a homologous compound such as acetamidine acetate or acetamidine hydrochloride yields the pyrimidinedione V. With phosphorus oxychloride there is obtained therefrom the dichloro compound VI which yields compound II upon reaction with compound VII. All of these reactions are standard operations and can be carried out under conditions which are usual for such reactions and which are familiar to a person skilled in the art. Compounds IV in which R^5 represents a residue (a) can be obtained from corresponding phenylacetic acid esters of the formula R^6CH_2COOEt by reaction with diethyl carbonate in the presence of sodium ethylate. Compounds IV in which R^5 represents a residue (b) can be prepared by Knoevenagel condensation of diethyl malonate with a corresponding aldehyde R^6CHO and subsequent hydrogenation of the condensation product.

The inhibitory activity of the compounds of formula I on endothelin receptors can be demonstrated using the test procedures described hereinafter:

1 Inhibition of endothelin binding to human placenta membranes (see Life Sci 44:1429 (1989)

Human placenta is homogenized in 5 mM Tris buffer, pH 7.4, which contains 1 mM $MgCl_2$ and 250 mM sucrose. The homogenate is centrifuged at 4°C for 15 minutes at 3000 g, the supernatant containing the plasma membrane fractions is centrifuged for 30 minutes at 72000 g and the precipitate obtained from in each case 10 g of original tissue is suspended in 1 ml of 75 mM Tris buffer, pH 7.4, containing 25 mM $MgCl_2$ and 250 mM sucrose and freeze-dried at -20°C in 1 ml aliquots.

For the binding assay, the freeze-dried membrane preparations are thawed and, after centrifugation at 20°C for 10 minutes at 25000 g, re-suspended in assay buffer (50 mM Tris buffer, pH 7.4, containing 25 mM $MnCl_2$, 1 mM EDTA and 0.5% bovine serum albumin). 100 µl of this membrane suspension, containing 70 µg of protein, are incubated with 50 µl

of ^{125}I-endothelin (specific activity 2200 Ci/mMol) in assay buffer (25000 cpm, final concentration 20 pM) and 100 µl of assay buffer which contains varying concentrations of the test compound. The incubation is carried out at 20°C for 2 hours or at 4°C for 24 hours. The separation of free and membrane-bound radioligands is carried out by filtration over a glass fibre filter.

The inhibitory activity of compounds of formula I determined in this test procedure is given in Table 1 as the IC_{50}, i.e. as the concentration [µM] which is required to inhibit the specific binding of ^{125}I-endothelin by 50%.

Table 1

Compound of Example	IC_{50} [µM]
1	5
5.4	3
6.3	1.6
6.4	2
6.6	0.5
8.3	0.7
8.4	1

11 Inhibition of endothelin-induced contractions in isolated aorta rings of the rat

Rings with a thickness of 5 mm were dissected from the thorax aorta of adult Wistar-Kyoto rats. The endothelium was removed by rubbing the internal surface slightly. Each ring was immersed in an isolated bath at 37°C in 10 ml of Krebs-Henseleit solution while gassing with 95% O_2 and 5% CO_2. The isometric tension of the rings was measured. The rings were stretched to an initial tension of 3 g. After incubation with the test compound or vehicle for 10 minutes cumulative doses of endothelin-1 were added. The activity of the test compound was determined by calculating the dosage ratio, i.e. the correcting shift (shift to higher values) of the EC_{50} of endothelin induced by 100 µm of test compound, whereby EC_{50} denotes the endothelin concentration

required for a half-maximum contraction. The greater this dosage ratio is, then the more potent is the inhibition of the test compound of the biological activity of endothelin-1. The EC_{50} of endothelin in the absence of test compounds is 0.3 nM.

The values for the correcting shift of the EC_{50} of endothelin thus obtained with compounds of I are given in Table 2.

Table 2

Compound of Example	Dosage ratio (correcting shift)
1	30
5.4	21
6.3	23
6.4	19
6.6	96
8.3	86
8.4	106

III. The inhibitory activity of the compounds of formula I on vasoconstriction can be observed in vivo in the rat in the test procedure described hereinafter:

Rats were anaesthetised with Na thiobutabarbital (100 mg/kg i.p.). A catheter was placed through the femoral artery in order to measure the systemic arterial blood pressure and a catheter was placed in the inferior vena cava via the femoral vein for the injection of the test compounds. A Doppler probe was placed around the left renal artery and attached to a Doppler measuring device. A renal ischemia was produced by pinching off the left renal artery at its point of emergence for 45 minutes. The test compounds were administered 10 minutes prior to the onset of the ischemia intraarterially (i.a.) in doses of 5 mg/kg or intravenously (i.v) in doses of 10 mg/kg. In control experiments the renal blood flow was reduced by 43±4% in comparison to the pre-ischemic value.

The results obtained with two compounds of formula I are given in Table 3.

Table 3

Compound of Example	% Decrease in the renal blood flow
1 i.a.	-
83 i.v.	29

Having regard to their capability of inhibiting endothelin binding, the compounds of formula I can be used as agents for the treatment of illnesses which are associated with processes which increase vasoconstriction. Examples of such illnesses are high blood pressure, coronary diseases, cardiac insufficiency, renal and myocardial ischemia, renal insufficiency, dialysis, cerebral ischemia, cardiac infarct, migraine, subarachnoid haemorrhage, Raynaud syndrome and pulmonary high pressure. They can also be used in atherosclerosis, the prevention of restenosis after balloon-induced vessel dilation, inflammations, gastric and duodenal ulcers, ulcus cruris, gram-negative sepsis, shock, glomerulonephritis, renal cholic, glaucoma, asthma, in the theraphy and prophylaxis of diabetic complications and complications with the administration of cyclosporin as well as other illnesses which are associated with endothelin activities.

The compounds of formula I can be administered orally, rectally, parenterally, e.g. intravenously, intramuscularly, subcutaneously, intrathecally or transdermally; or sublingually or as ophthalmological preparations, or as aerosols. Capsules, tablets, suspensions or solutions for oral administration, suppositories, injection solutions, eye drops, salves or spray solutions are examples of administration forms.

Intravenous, intramuscular or oral administration is a preferred form of use. The dosage in which the compounds of formula I are administered in effective amounts depends on the nature of the specific active ingredient, the age and the require-

ments of the patient and the mode of administration. In general, doses of about 0.1-100 mg/kg body weight per day come into consideration. The preparations containing the compounds of formula I can contain inert as well as pharmacodynamically active additives. Tablets or granulates e.g. can contain a series of binders, fillers, carriers or diluents. Liquid preparations can be present, for example, in the form of a sterile water-miscible solutions. Capsules can contain a filler or thickener in addition to the active ingredient. Furthermore, flavour improving additives as well as substances usually used as preserving, stabilizing, moisture-retaining and emulsifying agents as well as salts for varying the osmotic pressure, buffers and other additives can be present.

The previously mentioned carriers and diluents can comprise organic or inorganic substances, e.g. water, gelatine, lactose, starch, magnesium stearate, talc, gum arabic, polyalkylene glycols and the like. It is a prerequisite that all aduvants used in the manufacture of the preparations are non-toxic.

Example 1

A solution of 0.046 g of Na in 1.5 ml of abs. ethylene glycol was treated with 0.216 g of N-[6-chloro-5-(p-chlorophenyl)-4-pyrimidinyl]-α,α,α-trifluoro-p-toluenesulphonamide with the exclusion of moisture and heated at 100°C for 3 hours, thereafter cooled to room temperature and treated with 2.3 ml of 1N HCl. The mixture was taken up in ethyl acetate, the organic extracts were washed with water, dried and evaporated under reduced pressure. The precipitate remaining behind was recrystallized from CH_2Cl_2, isopropyl ether and n-hexane and yielded N-[5-(p-chlorophenyl)-6-(2 hydroxyethoxy)-4-pyrimidinyl]-α,α,α-trifluoro-p-toluenesulphonamide, melting point 160-162°C

The starting material was prepared as follows:

A solution of 1.052 g of α,α,α-trifluorobenzenesulphonamide potassium and 0.520 g of 4,6-dichloro-5-(p-chloro-

phenyl)pyrimidine (Chem. Abstr. 63, 18078-HO-a) in 6 ml of abs. DMF was heated at 100°C for 4 hours, thereafter cooled to room temperature and treated with 5 ml of 1N HCl. The mixture was taken up in ethyl acetate, the organic extracts were washed with water, dried and evaporated under reduced pressure. There was obtained N-[6-chloro-5-(p-chlorophenyl)-4-pyrimidinyl]-α,α,α-trifluoro-p-toluenesulphonamide as a white substance of melting point 275°C (from acetonitrile).

Example 2

In analogy to Example 1, from N-[6-chloro-5-(p-chlorophenyl)-4-pyrimidinyl]-p-(trifluoromethoxy)benzenesulphonamide and ethylene glycol Na there was obtained N-[5-(p-chlorophenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]-p-(trifluoromethoxy)benzenesulphonamide, melting point 152°C (from isopropyl ether).

The starting material was obtained from 4,6-dichloro-5-(p-chlorophenyl)-pyrimidine and p-(trifluoromethoxy)benzenesulphonamide potassium, melting point 240-242°C.

Example 3

In analogy to Example 1, from p-chloro-N-[6-chloro-5-(m-chlorophenyl)-4-pyrimidinyl]benzenesulphonamide and ethylene glycol Na there was obtained p-chloro-N-[5-(m-chlorophenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]benzenesulphonamide melting point 178-180°C (from acetone-isopropyl ether).

The starting material was prepared as follows:

a) 5.97 g of formamidine acetate were added to a solution of 3.96 g of Na and 100 ml of abs. methanol. After cooling the solution to 10°C 15.51 g of diethyl (m-chlorophenyl)malonate were added in portions. After 2.5 hours the solvent was evaporated under reduced pressure, the residue was dissolved in water and the solution was adjusted to pH 5.0 with glacial acetic

acid. The resulting precipitate was filtered off under suction, washed with water, ethanol and ether and dried at 70°C under reduced pressure. There was obtained 5-(m-chlorophenyl)-4,6(1H,5H)-pyrimidinedione which was used directly in the next step.

b) A mixture of 10.6 g of 5-(m-chlorophenyl)-4,6(1H,5H)-pyrimidinedione, 36 ml of $POCl_3$ and 5.8 ml of N,N-dimethylaniline was boiled at reflux for 3 hours. After evaporation of the solvent under reduced pressure the residue was treated with ice and the mixture was extracted with ether. The organic solvent was dried and evaporated under reduced pressure The oily residue was taken up in n-hexane, whereby 4,6-dichloro-5-(m-chlorophenyl)-pyrimidine crystallized out. Melting point 93-94°C.

c) From 4,6-dichloro-5-(m-chlorophenyl)-pyrimidine and p-chlorobenzenesulphonamide K there was obtained p-chloro-N-[6-chloro-5-(m-chlorophenyl)-4-pyrimidinyl]benzenesulphonamide, melting point 226-228°C (from CH_3CN).

Example 4

In analogy to Example 1, from p-chloro-N-[6-chloro-5-(p-fluorophenyl)-4 pyrimidinyl]benzenesulphonamide there was obtained p-chloro-N-[5-(p-fluorophenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]benzenesulphonamide, melting point 208-212°C (from CH_3CN).

The starting material was prepared as follows:

a) In analogy to Example 3, paragraph a), from diethyl (p-fluorophenyl)malonate and formamidine acetate there was obtained 5-(p-fluorophenyl)-4,6(1H,5H)-pyrimidinedione as a solid which was used directly in the next step.

b) In analogy to Example 3, paragraph b) from 5-(p-fluorophenyl)-4,6(1H,5H)-pyrimidinedione and $POCl_3$ there was

obtained 4,6-dichloro-5-(p-fluorophenyl)pyrimidine, melting point 98-99°C (from n-hexane).

c) In analogy to Example 3, paragraph c), from 4,6-dichloro-5-(p-fluorophenyl)pyrimidine and p-chlorophenylsulphonamide K there was obtained p-chloro-N-[6-chloro-5-(p-fluorophenyl)-4-pyrimidinyl]benzenesulphonamide, melting point 251-254°C (from methylene chloride-isopropyl ether).

Example 5

In analogy to Example 1, from N-(6-chloro-5-(p-chlorophenyl)-4-pyrimidinyl]-p-fluorobenzenesulphonamide and ethylene glycol Na there was obtained N-[5-(p-chlorophenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]-p-fluorobenzenesulphonamide, melting point 181-183°C (from methylene chloride-isopropyl-ether).

The starting material was prepared from 4,6-dichloro-5-(p-chlorophenyl)pyrimidine and p-fluorophenylsulphonamide. Melting point 244-246°C (from methylene chloride-isopropyl ether).

Example 6

In analogy to Example 1, from o-chloro-N-[6-chloro-5-(p-chlorophenyl)-4-pyrimidinyl]benzenesulphonamide and ethylene glycol Na there was obtained o-chloro-N-[5-(p-chlorophenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]benzenesulphonamide, melting point 183-185°C (from acetone and isopropyl ether).

The starting material was obtained from 4,6-dichloro-5-(p-chlorophenyl)pyrimidine and o-chlorophenylsulphonamide. Melting point 230-234°C (from CH_3CN).

Example 7

In analogy to Example 1, from N-[6-chloro-5-(p-ethylphenyl)-4-pyrimidinyl]-p-cyclopentylbenzenesulphonamide and ethylene glycol Na there was obtained p-cyclopentyl-N-[6-(2-hydroxyethoxy)-5-(p-ethylphenyl)-4-pyrimidinyl]benzenesulphon- amide, melting point 145-146°C (from acetone and isopropyl ether).

The starting material was prepared from 4,6-dichloro-5-(p-ethylphenyl)pyrimidine and p-cyclopentylbenzenesulphonamide, melting point 178-180°C (from acetonitrile and isopropyl ether).

Example 8

In analogy to Example 1, from p-chloro-N-[6-chloro-5-(3,4-dimethoxyphenyl)-4-pyrimidinyl]benzenesulphonamide and ethylene glycol Na there was obtained p-chloro-N-[5-(3,4-dimethoxyphenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]benzenesulphonamide, melting point 232-234°C (from CH_3CN).

The starting material was prepared as follows:

In analogy to Example 3, paragraph b), from 5-(3,4-dimethoxyphenyl)-4,6(1H,5H)-pyrimidinedicne and $POCl_3$ there was prepared 4,6-dichloro-5-(3,4-dimethoxyphenyl)pyrimidine, melting point 151-152°C (from cyclohexane-ether),from which with p-chlorophenylsulphonamide there was obtained p-chloro-N-[6-chloro-5-(3,4-dimethoxyphenyl)-4-pyrimidinyl]benzenesulphonamide, melting point 201-203°C (from CH_3CN).

Example 9

In analogy to Example 1, from 3,4 dichloro-N-[6-chloro-5-(p-chlorophenyl)pyrimidinyl]benzenesulphonamide and ethylene glycol Na there is obtained 3,4-dichloro-N-[5-(p-chlorophenyl)-6-

(2-hydroxyethoxy)-4-pyrimidinyl]benzenesulphonamide, melting point 181°C (from CH_3CN and isopropyl ether).

Example 10

In analogy to Example 1, from N-[6-chloro-5-(p-chlorophenyl)-4-pyrimidinyl]-α,α,α,α',α',α'-hexafluoromethyl-xylenesulphonamide there was obtained N-5-(p-chlorophenyl)-6-(2-hydroxyethoxy)-4 pyrimidinyl]-α,α,α,α',α',α'-hexafluoro-3,5-xylenesulphonamide, melting point 156-158°C (from methylene chloride/n-hexane).

The starting material was prepared from 4,6-dichloro-5-(p-chiorophenyl)pyrimidine and 2,4-bis-trifluoromethyl-phenyl-sulphonamide. Melting point 132-135°C (from isopropyl ether); purity 92% (HPLC analysis).

Example 11

In analogy to Example 1, from 3-chloro-N-[6-chloro-5-(p-chlorophenyl)-4-pyrimidinyl]-4-fluorobenzenesulphonamide and an excess of ethylene glycol Na there was obtained 3-chloro-N-[5-(p-chlorophenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]-4-(2-hydroxyethoxy)benzenesulphonamide, melting point 138-140°C (from acetone-isopropyl ether).

The starting material was prepared from 4,6-dichloro-5-(p-chlorophenyl)pyrimidine and 3-chloro-4-fluorophenyl-sulphonamide. Melting point 239°C (from methylene chloride-acetonitrile).

Example 12

In analogy to Example 1, from p-chloro-N-(6-chloro-5-(p-nitrophenyl)-4-pyrimidinyl]benzenesulphonamide and ethylene glycol Na there was obtained p-chloro-N-(6-(2-hydroxyethoxy)-5-(p-nitrophenyl)-4-pyrimidinyl]benzenesulphonamide, melting point 223-225°C (from methylene chloride-isopropyl ether).

The starting material was prepared from 4-chloro-5-(p-nitrophenyl)pyrimidine and p-chlorophenylsulphonamide; melting point 282-285°C (from CH_3CN).

Example 13

In analogy to Example 1, from p-butoxy-N-[6-chloro-5-(p-chlorophenyl)-4-pyrimidinyl]benzenesulphonamide and ethylene glycol Na there was obtained p-butoxy-N-[5-(p-chlorophenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]benzenesulphonamide, melting point >300°C (from isopropyl ether), purity 97.7% by HPLC analysis.

The starting material was prepared from 4,6-dichloro-5-(p-chlorophenyl)pyrimidine and 4-n-butoxyphenylsulphonamide. Melting point 234°C (from CH_3CN).

Example 14

In analogy to Example 1, from N-6-chloro-[5-(p-chlorophenyl)-4-pyrimidinyl]-3,4-dimethoxybenzenesulphonamide and ethylene glycol Na there was obtained N-[5-(p-chlorophenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]-3,4-dimethoxybenzenesulphonamide, melting point 130-132°C (from isopropyl ether).

The starting material was prepared from 4,6-dichloro-5-(p-chlorophenyl)pyrimidine and 3,4-dimethoxyphenylsulphonamide. Melting point 226°C (from CH_3CN).

Example 15

In analogy to Example 1, from o-chloro-N-[6-chloro-5-(p-chlorophenyl)-4-pyrimidinyl]-α,α,α-trifluoro-p-toluenesulphonamide and ethylene glycol Na there was obtained 2-chloro-N-[5-(p-chlorophenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]-α,α,α-trifluoro-p-toluenesulphonamide, melting point 131°C (from isopropyl ether).

The starting material was prepared from 4,6-dichloro 5-(p-chlorophenyl)pyrimidine and 2-chloro-α,α,α-trifluoro-p-toluenesulphonamide; melting point 234°C (from methylene chloride-acetonitrile).

Example 16

In analogy to Example 1, from 6-chloro-N-[6-chloro-5-(p-chlorophenyl)-4-pyrimidinyl]-α,α,α-trifluoro-m-toluene-sulphonamide and ethylene glycol Na there was obtained 6-chloro-N-[5-(p-chlorophenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]-α,α,α-trifluoro-m-toluenesulphonamide, melting point 185-186°C (from isopropyl ether).

The starting material was prepared from 4,6-dichloro-5-(p-chlorophenyl)pyrimidine and α,α,α-trifluoro-3-methyl-6-chlorophenylsulphonamide; melting point 232°C (from isopropyl ether).

Example 17

In analogy to Example 1, from 2,3,4-trichloro-N-[6-chloro-5-(p-chlorophenyl)-4-pyrimidinyl]benzenesulphonamide and ethylene glycol Na there was obtainded 2,3,4-trichloro-N-[(5-chlorophenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]benzene-sulphonamide, melting point 209-211°C (from methylene chloride-isopropyl ether).

The starting material was prepared from 4,6-dichloro-5-(p-chlorophenyl)pyrimidine and 2,3,4-trichlorophenylsulphon-amide; melting point 278-280°C (from CH_3CN).

Example 18

In analogy to Example 1 from m-chloro-N-[6-chloro-5-(p-chlorophenyl)-4-pyrimidinyl]benzenesulphonamide and ethylene glycol Na there was obtained m-chloro-N-(p-chlorophenyl)-6-(2-

hydroxyethoxy)-4-pyrimidinyl]benzenesulphonamide, melting point 179-181°C (from acetonitrile-isopropyl ether).

The starting material was prepared from 4,6-dichloro-5-(p-chlorophenyl)pyrimidine and 3-chlorophenylsulphonamide; melting point 219-221°C (from CH_3CN).

Example 19

In analogy to Example 1, from 2,4-dichloro-N-[6-chloro-5-(p-chlorophenyl)-4-pyrimidinyl]benzenesulphonamide and ethylene glycol Na there was obtained 2,4-dichloro-N-[5-(p-chlorophenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]benzene-sulphonamide, melting point 165-167°C (from CH_3CN).

The starting material was prepared from 4,6-dichloro-5-(p-chlorophenyl)pyrimidine and 2,4-dichlorophenylsulphonamide; melting point 252-254°C (from CH_3CN).

Example 20

In analogy to Example 1, from N-6-chloro-5-(p-chloro-phenyl)-α,α,α-trifluoro-m-toluenesulphonamide and ethylene glycol Na there was obtained N-5-(p-chlorophenyl)-6-(2-hydroxyethoxy)-α,α,α-trifluoro-m-toluenesulphonamide, melting point 148-150°C (from isopropyl ether).

The starting material was prepared from 4,6-dichloro-5-(p-chlorophenyl)pyrimidine and α,α,α-trifluoro-m-toluene-sulphonamide; melting point 197-198°C.

Example 21

In analogy to Example 1, from N-6-chloro-5-(p-chloro-phenyl)-α,α,α-trifluoro-o-toluenesulphonamide and ethylene glycol Na thee was obtained N-5-(p-chlorophenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]-α,α,α-trifluoro-o-toluene-

sulphonamide; melting point 182-184°C (from CH_3CN-isopropyl ether).

The starting material was prepared from 4,6-dichloro-5-(p-chlorophenyl)pyrimidine and α,α,α-trifluoro-o-toluenesulphonamide; melting point 191-193°C (from CH_3CN).

Example 22

In analogy to Example 1, from N-[6-chloro-5-(p-ethylphenyl)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide and ethylene glycol Na there was obtained N-[6-(2-hydroxyethoxy)-5-(p-ethylphenyl)-4-pyrimidinyl]-p-isopropyl]benzenesulphonamide, melting point 137-138°C (from acetonitrile and isopropyl ether).

The starting material was prepared as follows:

From diethyl (p-ethylphenyl)malonate and formamidine acetate there was obtained 5-(p-ethyl)-4,6(1H,5H)-pyrimidinedione, melting point >270°C, and therefrom with $POCl_3$ there was obtained 4,6-dichloro-5-(p-ethylphenyl)pyrimidine, melting point 48-49°C (from n-hexane).

Reaction of this compound with p-isopropylbenzenesulphonamide yielded N-[6-chloro-5-(p-ethylphenyl)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide, melting point 187-188°C (from acetonitrile and isopropyl ether).

Example 23

In analogy to Example 1, from N chloro-5-(p-chlorophenyl)-4-pyrimidinyl]-2-naphthalenesu onamide and ethylene glycol Na there was obtained -[5-(p-chlorophenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]-2-na halenesulphonamide, melting point 196-198°C (from CH_3CN a. isopropyl ether).

The starting material was prepared from 4,6-dichloro-5-(p-chlorophenyl)pyrimidine and 2-naphthalenesulphonamide; melting point 265-269°C (from CH_3CN).

Example 24

In analogy to Example 1, from p-chloro-N-[6-chloro-5-(m-nitrophenyl)-4-pyrimidinyl]benzenesulphonamide and ethylene glycol Na there was obtained p-chloro-N-[6-(2-hydroxyethoxy)-5-(m-nitrophenyl)-4-pyrimidinyl]benzenesulphonamide, melting point 186-187°C (from CH_3CN and isopropyl ether).

The starting material was prepared from 4,6-dichloro-5-(m-nitrophenyl)pyrimidine and p-chlorophenylsulphonamide; melting point 261-263°C (from CH_3CN).

Example 25

In analogy to Example 1, from N-[6-chloro-5-(m-nitrophenyl)-4-pyrimidinyl]-α,α,α-trifluoro-p-toluenesulphonamide and ethylene glycol Na there was obtained α,α,α-trifluoro-N-[6-(2-hydroxyethoxy)-5-(m-nitrophenyl)-4-pyrimidinyl]-p-toluenesulphenamide, melting point 194-195°C (from ethyl acetate/n-hexane).

The starting material was prepared from 4,6-dichloro-5-(m-nitrophenyl)pyrimidine and α,α,α-trifluoro-p-toluenesulphonamide; melting point 246-250°C (from CH_3CN).

Example 26

In analogy to Example 1, from p-(benzyloxy)-N-[6-chloro-5-(p-chlorophenyl)-4-pyrimidinyl]benzenesulphonamide and ethylene glycol Na there was obtained p-(benzyloxy)-N-[5-(p-chlorophenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]benzenesulphonamide, melting point 162-163°C (from acetone and isopropyl ether).

The starting material was prepared from 4,6-dichloro-5-(p-chlorophenyl)pyrimidine and p-(benzyloxy)benzenesulphonamide; melting point 233-236°C (from acetone and ethyl acetate).

Example 27

A solution of 512 mg of p-(benzyloxy)-N-[5-(p-chlorophenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]benzenesulphonamide in 30 ml of glacial acetic acid was treated with 2 ml of 4N HCl in dioxan and 100 mg of 10% palladium-carbon. The mixture was hydrogenated while stirring, thereafter the solution was suction filtered, evaporated under reduced pressure and the residue was recrystallized from isopropyl ether and again from CH_3CN. There was obtained N-[5-(p-chlorophenyl)-4-pyrimidinyl]-p-hydroxybenzenesulphonamide, melting point 231-232°C.

Example 28

In analogy to Example 1, from N-[6-chloro-5-(p-chlorophenyl)-4-pyrimidinyl]-p-(2-methoxyethoxy)benzenesulphonamide and ethylene glycol Na there was obtained N-[5-(p-chlorophenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]-p-(2-methoxyethoxy)benzenesulphonamide, melting point 151-152°C (from CH_3CN and isopropyl ether).

The starting material was prepared from 4,6-dichloro-5-(p-chlorophenyl)pyrimidine and p-(2-methoxyethoxy)benzenesulphonamide; melting point 212-215°C (from CH_3CN).

Example 29

In analogy to Example 1, from N-[5-(p-bromophenyl)-6-chloro-4-pyrimidinyl]-p-chlorobenzenesulphonamide and ethylene glycol Na there was obtained N-[5-(p-bromophenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]-p-chlorobenzenesulphonamide, melting point 179-180°C (from acetone and isopropyl ether).

The starting material was prepared as follows:

In analogy to Example 3, paragraph a), from diethyl p-bromophenylmalonate and formamidine acetate there was obtained 5-(p-bromophenyl)-4,6(1H,5H)-pyrimidinedione, melting point >270°C. The compound was used in the next step after drying under reduced pressure at 80°C overnight.

In analogy to Example 3, paragraph b), from 5-(p-bromophenyl)-4,6(1H,5H)-pyrimidinedione and $POCl_3$ there was prepared 5-(p-bromophenyl)-4,6-dichloropyrimidine, melting point 99-100°C (from hexane), and therefrom with p-chlorophenylsulphonamide there was prepared N-[5-(p-bromophenyl)-6-chloro-4-pyrimidinyl]-p-chlorobenzenesulphonamide, melting point 266-268°C (from CH_3CN).

Example 30

In analogy to Example 1, from p-chloro-N-(6-chloro-5-p-tolyl-4-pyrimidinyl)benzenesulphonamide and ethylene glycol Na there was obtained p-chloro-N-[6-(2-hydroxyethoxy)-5-p-tolyl-4-pyrimidinyl]benzenesulphonamide, melting point 162-165°C (from acetone and isopropyl ether).

The starting material was prepared as follows:

In analogy to Example 3, paragraph a), from diethyl p-tolylmalonate and formamidine acetate there was prepared 5-p-tolyl-4,6(1H,5H)-pyrimidinedione, melting point >270°C. The substance was used in the next step after drying under reduced pressure at 80°C.

In analogy to Example 3, paragraph b), from 5-p-tolyl-4,6(1H,5H)-pyrimidinedione and $POCl_3$ there was prepared 4,6-dichloro-5-p-tolylpyrimidine, melting point 81-82°C (from hexane), and therefrom with p-chlorophenylsulphonamide there

was prepared p-chloro-N-(6-chloro-5-p-tolyl-4-pyrimidinyl)-benzenesulphonamide, melting point 229-230°C (from acetonitrile).

Example 31

A solution of 237 mg of N-[5-(p-chlorophenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]-α,α,α-trifluoro-p-toluene-sulphonamide in 5 ml of methanol was treated with 27.0 mg of sodium methylate and thereafter with 5 ml of isopropyl ether. The white precipitate was filtered off under suction and dried at 50°C under reduced pressure. There was obtained N-[5-(p-chlorophenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]-α,α,α-trifluoro-p-toluenesulphonamide sodium salt as a white solid.

Example 32

60 mg of sodium were added to 2 ml of ethylene glycol at 70°C. Thereafter, 223 mg of N-[6-chloro-5-(2,6-dimethoxy-benzyl)-4-pyrimidinyl]-p-vinyl-benzenesulphonamide were added and the reaction mixture was heated at 150°C for 4.5 hours. The ethylene glycol was distilled off under reduced pressure, the residue was taken up in EtOAc/H_2O and extracted once with ethyl acetate. Thereafter, the aqueous phase was acidified with 1N HCl and extracted four times with ethyl acetate. The organic phase was dried, filtered and concentrated under reduced pressure. The residue was chromatographed over 50 g of SiO_2 with methylene chloride/ethyl acetate 1:1. There were obtained 50 mg of N-[5-(2,6-dimethoxybenzyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]-p-vinylbenzenesulphonamide, melting point 138-139°C.

The starting material was prepared as follows:

a) A mixture of 1.52 ml of diethyl malonate, 1.66 g of 2,6-dimethoxybenzaldehyde, 0.1 ml of piperidine, 0.11 ml of glacial acetic acid and 100 ml of toluene was boiled at 110°C on a water separator for 3.5 hours. The solution was extracted with

10% $NaHCO_3$ solution and back-washed with saturated NaCl solution. The organic phase was dried, filtered off under suction and evaporated under reduced pressure. There were obtained 2.8 g of diethyl (2,6-dimethoxybenzylidene)malonate as a dark yellow oil.

b) A mixture of 2.8 g of diethyl (2,6-dimethoxybenzylidene)-malonate, 0.6 g of palladium-carbon, 50 ml of methanol and 50 ml of glacial acetic acid was stirred at 25°C overnight. The solution was filtered and concentrated, and the residue was taken up in ethyl acetate and extracted with 20% $NaHCO_3$ and some ice. Thereafter, the mixture was extracted with 1N HCl, back-washed with saturated NaCl solution, the organic phase was dried and evaporated under reduced pressure. The crude product was distilled in a high vacuum at 170°C/0.6 mbar. 2.1 g of diethyl (2,6-dimethoxybenzyl)malonate were obtained.

c) 0.23 g of formamidine acetate in 15 ml of ethanol was added to 0.14 g of sodium in 15 ml of ethanol. The reaction mixture was stirred 25°C for 30 minutes and treated dropwise with 0.62 g of diethyl (2,6-dimethoxybenzyl)malonate in 10 ml of ethanol. Starting material was no longer present after 2 days. The residue was filtered off under suction, dissolved in a small amount of water and acidified with 1N HCl. The precipitated crystals were filtered off under suction and dried at 90°C in a high vacuum. There was obtained 0.175 g of 5-(2,6-dimethoxy-benzyl)-4,6-pyrimidinediol of melting point >245°C.

d) A mixture of 1.04 g of 5-(2,6-dimethoxybenzyl)-4,6-pyrimidinediol and 12 ml of phosphorus oxychloride was boiled at reflux at 85°C for 3 hours. The reaction solution was poured on to ice and extracted twice with methylene chloride. The organic phase was back-washed with saturated NaCl solution, dried, filtered off and concentrated under reduced pressure. The crude product was recrystallized from toluene/n-hexane. There was obtained 0.41 g of 4,6-dichloro-5-(2,6-dimethoxybenzyl)-pyrimidine, melting point 152-153°C.

e) A mixture of 80 mg of 4,6-dichloro-5-(2,6-dimethoxy-benzyl)pyrimidine and 170 mg of p-vinylbenzenesulphonamide monopotassium salt (J. Am. Chem. Soc. 1956, 78, 2169) from the corresponding sulphonamide with potassium t-butylate in abs. MeOH and 10 ml of dimethylformamide was heated at 100°C for 6 hours. Thereafter, the mixture was left to cool to 25°C overnight. Now, 30 ml of 0.5N HCl were added to the reaction solution while stirring. The precipitated substance was filtered off under suction and recrystallized from toluene/n-hexane. There were obtained 25 mg of N-(6-chloro-5-(2,6-dimethoxy- benzyl)-4-pyrimidinyl)-p-vinylbenzenesulphonamide, melting point 197-198°C.

Example 33

29 mg of sodium were added portionwise to 10 ml of ethylene glycol (freshly distilled over Na) while excluding moisture. Thereafter, 123 mg of N-[6-chloro-6-[o-(trifluoro-methyl)benzyl]-4-pyrimidinyl]-α,α,α-trifluoro-p-toluenesulphonamide were added and the reaction mixture was heated at 150°C for 3 hours. Thereafter, the excess ethylene glycol was evaporated under reduced pressure; the residue was dissolved in water and washed with ethyl acetate. The aqueous phase was adjusted to pH 3.0 with 1N hydrochloric acid and extracted with ethyl acetate. The organic phase was washed with water and saturated sodium chloride solution, dried and evaporated under reduced pressure. The residue was chromatographed over 30 g of SiO_2 with methylene chloride/ethyl acetate (1:1). There was obtained α,α,α-trifluoro-N-[6-(2-hydroxyethoxy)-6-[o-(trifluoro-methyl)benzyl]pyrimidinyl]-p-toluenesulphonamide as a white foam. MS: 521 (M); 456 (M-SO_2+H).

The starting material was prepared as follows:

a) A solution of 30 ml of phosphorus tribromide in 60 ml of abs. toluene was added dropwise at 20-30°C to a solution of 14 g of o-trifluoromethylbenzyl alcohol in 80 ml of abs. toluene. Subsequently, the reaction mixture was stirred at room

temperature for 2 hours, the toluene was distilled off under reduced pressure, the residue was dissolved in methylene chloride, treated with water and the mixture was adjusted to pH 8.0 with potassium hydrogen carbonate. The aqueous phase was extracted three times with CH_2Cl_2 and the organic phases were washed twice with water and once with saturated NaCl solution, dried over Na_2SO_4 and evaporated under reduced pressure. o-Trifluoromethylbenzyl bromide was obtained as the residue.

b) 40 ml of diethyl malonate in 350 ml of ethyl alcohol were treated portionwise with 18.6 g of sodium ethylate at room temperature and the mixture was then treated with 12 g of o-trifluoromethylbenzyl bromide within 30 minutes. The reaction mixture was stirred at room temperature overnight, the alcohol was distilled off under reduced pressure and the residue was dissolved in ethyl acetate. The solution was washed twice with water and once with NaCl solution, dried under reduced pressure and evaporated. The residue was chromatographed over 300 g of SiO_2 with CH_2Cl_2/AcOEt 95:5 and yielded 11 g of diethyl [o-(trifluoromethyl)benzyl]malonate as a colourless oil.

c) 0.63 g of formamidine acetate in 40 ml of abs. ethyl alcohol was treated with 1.2 g of sodium ethylate at room temperature, stirred at room temperature for 30 minutes and then treated dropwise at room temperature with a solution of 1.6 g of diethyl [o-(trifluoromethyl)benzyl]malonate in 8 ml of abs. ethyl alcohol. After stirring at 50°C for 4 hours the reaction mixture was worked-up and yielded 5-[o-(trifluoromethyl)- benzyl]-4,6(1H,5H)pyrimidinedione, melting point >290°C.

d) From 5-[o-(trifluoromethyl)benzyl]-4,6(1H,5H)pyrimidine-dione and phosphorus oxychloride there was prepared 5-[o-(trifluoromethyl)benzyl]-4,6-dichloropyrimidine, melting point 60-63°C.

e) 295 mg of 4,6-dichloro-5-[o-(trifluoromethyl)benzyl]-pyrimidine in 10 ml of freshly distilled dimethyl sulphoxide were treated with 342 mg of α,α,α-trifluoro-p-toluene- sulphonamide

monopotassium salt (from the from the corresponding sulphonamide with KOH and abs. ethyl alcohol) and stirred at 150°C for 5 hours. After completion of the reaction the solvent was distilled off under reduced pressure, the residue was dissolved in ethyl acetate and the solution was washed with 10% potassium bicarbonate solution, 0.5N HCl, water and NaCl solution. The organic phase was dried and evaporated under reduced pressure. The residue was chromatographed over 30 g of SiO_2 using ethyl acetate and yielded 135 mg of N-[6-chloro-6-[o-(trifluoromethyl)benzyl]-4-pyrimidinyl]-α,α,α-trifluoro-p-toluenesulphonamide as a white foam. MS: 495 (M), 431 ($-SO_2$), 430 ($-SO_2+H$), 362 ($-CF_3+SO_2$).

Example 34

In analogy to Example 33, from N-[6-chloro-5-[o-(trifluoromethyl)benzyl]-4-pyrimidinyl]-p-methoxybenzenesulphonamide and ethylene glycol Na there was obtained N-[6-(2-hydroxyethoxy)-5-[o-(trifluoromethyl)benzyl]-4-pyrimidinyl]-p-methoxybenzenesulphonamide, melting point 100-107°C.

The starting material was prepared as follows:

In analogy to Example 33, paragraph e), from 4,6-dichloro-5-[o-(trifluoromethyl)benzyl]pyrimidine and p-methoxybenzenesulphonamide K salt there was obtained N-[6-chloro-5-[o-(trifluoromethyl)benzyl]-4-pyrimidinyl]-p-methoxybenzenesulphonamide as a white foam, melting point 68-70°C.

Example 35

In analogy to Example 33, from p-chloro-N-[6-chloro-5-[o-(trifluoromethyl)benzyl]-4-pyrimidinyl]benzenesulphonamide and ethylene glycol Na there was obtained p-chloro-N-[6-(2-hydroxyethoxy)-5-[o-(trifluoromethyl)benzyl]-4-pyrimidinyl]benzenesulphonamide, melting point 134-135°C.

The starting material was prepared in analogy to Example 33, paragraph e), from 4,6-dichloro-5-[o-(trifluoromethyl)benzyl]-

pyrimidine and p-chlorobenzenesulphonamide K salt; melting point >210°C (decomposition).

Example 36

In analogy to Example 33, from N-[6-chloro-5-(o-methoxybenzyl)-4-pyrimidinyl]-p-vinylbenzenesulphonamide and ethylene glycol Na there was obtained N-[6-(2-hydroxyethoxy)-5-(o-methoxybenzyl)-4-pyrimidinyl]-p-vinylbenzenesulphonamide, melting point 93-102°C.

The starting material was prepared in analogy to Example 33, paragraph e) from 4,6-dichloro-5-(o-methoxybenzyl)pyrimidine and p-vinylbenzenesulphonamide K salt; melting point 125-129°C.

Example 37

In analogy to Example 33, from N-[6-chloro-5-[o-(trifluoromethyl)benzyl]-4-pyrimidinyl]-p-(methylthio)benzenesulphonamide and ethylene glycol Na there was obtained N-[6-(2-hydroxyethoxy)-5-[o-(trifluoromethyl)benzyl]-4-pyrimidinyl]-p-(methylthio)benzenesulphonamide as a yellowish resin.

The starting material was prepared in analogy to Example 33, paragraph e), from 4,6-dichloro-5-[o-(trifluoromethyl)]benzyl-pyrimidine and p-(methylthio)benzenesulphonamide; IR: 3433 cm^{-1} (NH); 1313 (SO_2); 1137 and 1094 (F_3C).

Example 38

In analogy to Example 32, from N-[6-chloro-5-(2,4-dimethoxybenzyl)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide, ethylene glycol and sodium there was obtained N-[5-(2,4-dimethoxybenzyl)-6-(3-hydroxypropyl)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide, melting point 97°C.

The starting material was prepared as follows:

In analogy to Example 32, paragraph a), from 2,4-dimethoxybenzaldehyde, diethyl malonate, glacial acetic acid, piperidine and toluene there was prepared diethyl (2,4-dimethoxybenzyl-

idene)malonate. Therefrom in analogy to Example 32, paragraph b), there was prepared diethyl (2,4-dimethoxy-benzyl)malonate as a clear oil, boiling point 160°C/0.4 mbar.

In analogy to Example 32, paragraph e), from diethyl (2,4-dimethoxybenzyl)malonate, formamidine acetate and the Na salt of ethanol there was prepared 5-(2,4-dimethoxybenzyl)-4,6-pyrimidinediol and therefrom in analogy to Example 32, paragraph d), there was prepared 4,6-dichloro-5-(2,4-dimethoxybenzyl)-pyrimidine, melting point 130-131°C.

In analogy to Example 32, paragraph e), from 4,6-dichloro-5-(2,4-dimethoxybenzyl)pyrimidine, p-isopropylbenzenesulphonamide K (from the corresponding sulphonamide with potassium t-butylate in abs. MeOH) and DMSO there was finally prepared N-[6-chloro-5-(2,4-dimethoxybenzyl)-4-pyrimidinyl]-p-isopropyl-benzenesulphonamide, melting point 132-134°C.

Example 39

A solution of 110 mg of N-[6-(2-hydroxyethoxy)-5-(o-methoxybenzyl)-4-pyrimidinyl]-p-vinylbenzenesulphonamide in 3 ml of abs. tetrahydrofuran was treated with 0.3 ml of 3,4-dihydro-2H-pyran and 4 drops of trifluoroacetic acid. After boiling under reflux overnight the solvent was distilled off under reduced pressure and the residue was chromatographed on silica gel with methylene chloride/ethyl acetate (9:1). There were obtained 100 mg of rac-N-[5-(o-methoxybenzyl)-6-[2-[(tetrahydro-2H-pyran-2-yl)oxy]ethoxy]-4-pyrimidinyl]-p-vinylbenzenesulphonamide as a white resin. MS: 460 ($M-SO_2+H$); 430 ($M-SO_2+OCH_3$).

Example 40

318 mg of rac-N-[5-(o-methoxybenzyl)-6-[2-[(tetrahydro-2H-pyran-2-yl]oxy]ethoxy]-4-pyrimidinyl]-p-vinylbenzene-sulphonamide, 5.3 mg of osmium tetroxide and 270 mg of sodium(meta)periodate were added in succession to a mixture of 1.5 ml of water and 4 ml of dioxan at room temperature. After

stirring at room temperature for 1 hour the dioxan was distilled off under reduced pressure, thereafter the aqueous phase was extracted three times with ethyl acetate, the ethyl acetate was washed twice with water and once with NaCl solution (saturated), dried and distilled off under reduced pressure. The residue was chromatographed over 30 g of SiO_2 with CH_2Cl_2/ethyl acetate and yielded 150 mg of rac-p-[[5-(o-methoxybenzyl)-6-[2-[(tetrahydro-2H-pyran-2-yl)oxy]ethoxy]-4-pyrimidinyl]sulphamoyl]benzaldehyde as white foam. MS: 527 (M); 443 ( ); 432 (-OCH_3+SO_2).

Example 41

170 mg of rac-p-[[5-(o-methoxybenzyl)-6-[2-[(tetrahydro-2H-pyran-2-yl]oxy]ethoxy]-4-pyrimidinyl]sulphamoyl]benzaldehyde and, after 30 minutes, 1 ml of abs. tetrahydrofuran were added at room temperature to a Grignard solution prepared from 60 mg of magnesium and 0.15 ml of methyl iodide in diethyl ether. After stirring at room temperature for 3 hours the reaction was interrupted by the addition of saturated ammonium chloride solution, the reaction mixture was diluted with ethyl acetate and the aqueous phase was extracted twice with ethyl acetate. The organic phase was washed with water and saturated NaCl solution, dried and evaporated under reduced pressure. The residue was chromatographed over 35 g of SiO_2 with CH_2Cl_2/ethyl acetate (8:2) and (1:1) and yielded 135 mg of p-[(RS)-1-hydroxyethyl]-N-[5-(methoxybenzyl)-6-[2-[[(RS)-tetrahydro-2H-pyran-2-yl]oxy]ethoxy]-4-pyrimidinyl]benzene- sulphonamide melting point >56°C (sublimation).

Example 42

53 mg of rac-p-[[5-(o-methoxybenzyl)-6-[2-[(tetrahydro-2H-pyran-2-yl]oxy]ethoxy]-4-pyrimidinyl]sulphamoyl]benzaldehyde were dissolved in 3 ml of methyl alcohol and treated with 37 mg of sodium borohydride at room temperature. After stirring at room temperature for 1 hour the methanol was evaporated under reduced pressure, the residue was dissolved in

ethyl acetate, washed with water and NaCl solution (saturated), dried and distilled under reduced pressure. There were obtained 42 mg of rac-α-hydroxy-N-[5-(o-methoxybenzyl)-6-[2-[(tetrahydro-2H-pyran-2-yl)oxy]ethoxy]-4-pyrimidinyl]-p-toluenesulphonamide as a colourless oil. MS: 529 (M); 445 (tetrahydro-2H-pyran-2-yl); 434 ($-OCH_3+SO_2$).

Example 43

53 mg of rac-p-[[5-(o-methoxybenzyl)-6-[2-[(tetrahydro-2H-pyran-2-yl]oxy]ethoxy]-4-pyrimidinyl]sulphamoyl]benzaldehyde were dissolved in 3 ml of ethyl alcohol and treated at room temperature with 7 mg of hydroxylamine hydrochloride and 14 g of finely powd. potassium carbonate. After stirring at room temperature for 3 hours the ethanol was distilled off under reduced pressure, the residue was dissolved in ethyl acetate and washed with water and NaCl solution (saturated). The organic phase was dried and evaporated under reduced pressure, whereby rac-α-[(>E/Z)-hydroxyimino-N-[5-(o-methoxybenzyl)-6-[2-[(tetrahydro-2H-pyran-2-yl)oxy]ethoxy]-4-pyrimidinyl]-p-toluenesulphonamide, melting point 49-52°C, was obtained.

Example 44

A solution of 60 mg of p-[(RS-1-hydroxyethyl]-N-[5-(o-methoxybenzyl)-6-[2-[[(RS)-tetrahydro-2H-pyran-2-yl]oxy]-ethoxy]benzenesulphonamide in 3 ml of tetrahydrofuran was treated with 2 drops of 3N HCl. After stirring at room temperature for 4 hours the reaction mixture was evaporated under reduced pressure. The residue was chromatographed on silica gel with methylene chloride/ethyl acetate (1:1) and ethyl acetate and yielded rac-N-6-(2-hydroxyethoxy)-5-(o-methoxybenzyl)-p-(1-hydroxyethyl)benzenesulphonamide as a white resin. MS: 459 (M), 394 ($-SO_2/H$), 364 ($-SO_2/OCH_3$).

Example 45

In analogy to Example 44, from rac-a-[(E/Z)-hydroxyimino]-N-[5-(o-methoxybenzyl)-6-[2-[(tetrahydro-2H-pyran-2-yl)oxy]-ethoxy]-4-pyrimidinyl]-p-toluenesulphonamide there was obtained α-[(E/Z)-hydroxyimino]-N-[6-(2-hydroxyethoxy)-5-(o-methoxybenzyl)-4-pyrimidinyl]-p-toluenesulphonamide as a yellow resin. IR: 3403 and 3193 cm^{-1} (W, OH), 2607 (W, NH); 1729 (W, C=N).

Example 46

In analogy to Example 44, from rac-α-hydroxy-N-[5-(o-methoxybenzyl)-6-[2-[(tetrahydro-2H-pyran-2-yl)oxy]ethoxy]-4-pyrimidinyl]-p-toluenesulphonamide there was obtained α-hydroxy-N-[6-(2-hydroxyethoxy)-5-(o-methoxybenzyl)-4-pyrimidinyl]-p-toluenesulphonamide as a pale brown resin. MS: 445 (M), 380 (-SO_2/H), 274.

Example 47

In analogy to Example 44, from rac-p-[[5-(o-methoxy-benzyl)-6-[2-[(tetrahydro-2H-pyran-2-yl)oxy]ethoxy]-4-pyrimidinyl]-sulphamoylbenzaldehyde there was obtained p-[[6-(2-hydroxy-ethoxy)-5-(o-methoxybenzyl)-4-pyrimidinyl]-sulphamoyl]benzaldehyde as a while resin. MS: 443 (M), 348 (-SO_2/OCH_3), 274.

Example 48

208 mg of N-[6-(2-hydroxyethoxy)-5-(o-methoxybenzyl)-4-pyrimidinyl]-p-vinylbenzenesulphonamide were dissolved in 3 ml of abs. THF, treated with 0.06 ml of pyridine and 0.07 ml of acetic anhydride and boiled under reflux for 3 hours. After distilling off the solvent under reduced pressure the residue was dissolved in ethyl acetate, the solution was washed with water and sodium chloride solution, dried and evaporated. After chromatography over silica gel with methylene chloride and methylene chloride/ethyl acetate (19:1 and 9:1) the residue yielded 2-[[5-(o-methoxybenzyl)-6-[(p-vinylphenyl)sulphamoyl]-4-pyrimidinyl]oxy]ethyl acetate as a white resin.

Example 49

In analogy to Example 1, from N-[6-chloro-5-(α,α,α-trifluoro-p-tolyl)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide and ethylene glycol Na there was obtained N-[6-(2-hydroxyethoxy)-5-(α,α,α-trifluoro-p-tolyl)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide, melting point 222-223°C (from acetone and isopropyl ether).

The starting material was prepared from 4,6-dichloro-5-α,α,α-trifluoro-p-tolylpyrimidine and p-isopropylbenzenesulphonamide, melting point 266-269°C (from acetonitrile).

Example 50

190 mg of N-[6-chloro-5-(p-methoxyphenyl)-4-pyrimidinyl]-p-toluenesulphonamide were added to a sodium glycolate solution from 46 mg of sodium in 1 ml of ethylene glycol. After a reaction period of 5 hours at 100°C the reaction mixture was evaporated to dryness under reduced pressure, the residue was partitioned between ethyl acetate and 1N hydrochloric acid, the organic phase was washed neutral, dried and evaporated under reduced pressure. The residue was chromatographed on silica gel with methylene chloride and ethyl acetate (4:1 v/v). There were obtained 175 mg of N-[6-(2-hydroxyethoxy)-5-(p-methoxyphenyl)-4-pyrimidinyl]-p-toluenesulphonamide, melting point 147-149°C (from methylene chloride/hexane).

The starting material was prepared as follows:

150 ml of ethyl orthoformate and 1 g of methanesulphonic acid were added to a solution of 41.55 g of p-methoxyphenylacetic acid in 150 ml of abs. ethanol. The reaction mixture was heated at 85°C for 20 hours. The ethyl formate formed was distilled off continuously from the reaction mixture. Thereafter, the reaction mixture was neutralized with sodium ethylate, the

solvent was evaporated and the residue was taken up in methylene chloride and distilled. There were obtained 46.7 g of ethyl (p-methoxy)phenylacetate as a colourless liquid, boiling point 84°C/0.025 Torr.

7.5 g of sodium ethylate and 120 ml of diethyl carbonate were added to 19.4 g of the previously obtained ester. The suspension obtained was stirred vigorously at 130°C and the ethanol formed was distilled off from the reaction mixture. Thereafter, the reaction mixture was cooled to room temperature and poured on to ice and aqueous hydrochloric acid (10% excess). After extraction with ethyl acetate and working-up the extract the product was purified by distillation. There were obtained 25 g of diethyl (p-methoxy)phenylmalonate, boiling point 115°C/0.05 Torr.

10.9 g of sodium ethylate were suspended in 125 ml of dry ethanol. 4.83 g of formamidine hydrochloride and 13.3 g of the malonic ester obtained in the preceding paragraph were added thereto while cooling with ice. The reaction mixture was stirred at room temperature for 3 hours with the exclusion of moisture, thereafter the solvent was evaporated, the residue was dissolved in 100 ml of water, the aqueous phase was washed with toluene and acidified. There were obtained 8 g of 5-(p-methoxy)phenyl-6-hydroxy-4(3H)-pyrimidinone, melting point >250°C.

1 g of the pyrimidinone described in the foregoing paragraph was suspended in 5 ml of phosphorus oxychloride. The suspension was stirred at 80°C with the exclusion of moisture, whereby a clear solution was obtained. After 30 minutes the excess reagent was distilled off and the residue was taken up in methylene chloride and shaken with aqueous potassium hydrogen carbonate solution until the evolution of carbon dioxide no longer occurred. After evaporation of the solvent the residue was filtered over silica gel with methylene chloride. There was obtained 0.7 g of 4,6-dichloro-5-(p-methoxyphenyl)pyrimidine, melting point 95-96°C.

5.15 g of p-toluenesulphonamide dissolved in ethanol were added to a boiling ethanolic potassium hydroxide solution (2 g of 85% potassium hydroxide in 50 ml of abs. ethanol). Thereafter, 50 ml of abs. benzene were added and the majority of the solvent mixture was distilled off at normal pressure. 4.6 g of p-toluenesulphonamide potassium were obtained.

510 mg of the dichloropyrimidine described in the previous paragraph and 840 mg of p-toluenesulphonamide potassium were dissolved in 3 ml of dry dimethylformamide. The solution was held at 120°C for 3 hours, thereafter the dimethylformamide was distilled off, the residue was partitioned between ethyl acetate and 1N hydrochloric acid, the organic phase was washed neutral and evaporated. After the addition of methanol there were obtained 540 mg of N-[6-(chloro-5-(p-methoxyphenyl)-4-pyrimidinyl]-p-toluenesulphonamide, melting point 210-212°C.

Example 51

In analogy to Example 50, from 300 mg of N-[6-chloro-5-(p-methoxyphenyl)-4-pyrimidinyl]-p-methoxybenzenesulphonamide there were obtained 200 mg of N-[6-(2-hydroxyethoxy)-5-(p-methoxyphenyl)-4-pyrimidinyl]-p-methoxybenzenesulphonamide, melting point 132-134°C.

The starting material was prepared as follows:

25 ml of 25% NH_4OH were added dropwise while cooling in an ice bath to a solution of 7.3 g of p-methoxybenzenesulphonyl chloride in 50 ml of tetrahydrofuran. Subsequently, the reaction mixture was stirred vigorously for 30 minutes at 70°C (bath temperature), thereafter the tetrahydrofuran was distilled off. The residue was extracted with ethyl acetate. There was obtained p-methoxybenzenesulphonamide which was converted into the potassium salt as described in Example 50.

A solution of 510 mg of 4,6-dichloro-5-(p-methoxyphenyl)pyrimidine and 680 mg of p-

methoxybenzenesulphonamide potassium in 3 ml of dimethylformamide was heated at 130°C for 1 hour. After working-up the reaction mixture there were obtained 690 mg of N-[6-chloro-5-(p-methoxyphenyl)-4-pyrimidinyl]-p-methoxybenzenesulphonamide, melting point 165-167°C.

Example 52

In analogy to Example 50, from N-[6-chloro-5-(p-methoxyphenyl)-4-pyrimidinyl]-p-(methylthio)benzenesulphonamide there was obtained N-[6-(2-hydroxyethoxy)-5-(p-methoxyphenyl)-4-pyrimidinyl]-p-(methylthio)benzenesulphonamide, melting point 171-172°C.

The starting material was prepared as described in Example 50 from 4,6-dichloro-5-(p-methoxy)phenylpyrimidine and (p-methylthio)benzenesulphonamide potassium, melting point 204-205°C.

Example 53

In analogy to Example 50, from N-[6-chloro-5-(p-methoxyphenyl)-2-methyl-4-pyrimidinyl]-p-methoxybenzenesulphonamide there was obtained N-[6-(2-hydroxyethoxy)-5-(p-methoxyphenyl)-2-methyl-4-pyrimidinyl]-p-methoxybenzenesulphonamide, melting point 138-139°C.

The starting material was prepared as follows:

2.94 g of acetamidine hydrochloride and 6.9 g of diethyl p-methoxyphenylmalonate were added to a solution of 5.6 g of sodium methylate in 75 ml of abs. ethanol. The reaction mixture was stirred at room temperature for 3 hours with the exclusion of moisture and at 50°C for 1.5 hours. Thereafter, the ethanol was distilled off, the residue was taken up in water and the suspension was acidified with 5N hydrochloric acid. The solid was filtered off and washed with water until the wash solution had reached a pH of 4.5 to 5.7. The thus-obtained product was reacted with

phosphorus oxychloride and yielded 2.8 g of 4,6-dichloro-2-methyl-(p-methoxy)phenylpyrimidine, melting point 114-116°C. Reaction of this compound with p-methoxybenzene-sulphonamide potassium yielded N-[6-chloro-5-(p-methoxy-phenyl)-2-methyl-4-pyrimidinyl]-p-methoxybenzenesulphon-amide, melting point 152-154°C.

Example 54

In analogy to Example 50, from 615 mg of N-[6-chloro-5-(p-methoxyphenyl)-4-pyrimidinyl]-p-isopropylbenzenesulphon-amide there were obtained 550 mg N-[6-(2-hydroxyethoxy)-5-(p-methoxyphenyl)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide, melting point 128-129°C.

In order to convert this sulphonamide into the sodium salt, 87 mg were dissolved in methanol, the stoichiometric amount of sodium methylate was added, the solvent was distilled off and diisopropyl ether was added.

The starting material was prepared as follows:

p-Isopropylbenzenesulphonyl chloride, boiling point 105°C/0.25 Torr, was prepared from cumene and converted into the corresponding sulphonamide, melting point 104-105°C. Reaction of 765 mg of 4,6-dichloro-5-(p-methoxyphenyl)-pyrimidine and 925 mg of p-isopropylbenzenesulphonamide potassium yielded 720 mg of N-[6-chloro-5-(p-methoxyphenyl)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide, melting point 181-182°C.

Example 55

In analogy to Example 50, from 700 mg of p-t-butyl-N-[6-chloro-5-(p-methoxyphenyl)-4-pyrimidinyl]benzenesulphonamide there were obtained 600 mg of p-t-butyl-N-[6-(2-hydroxy-ethoxy)-5-(p-methoxyphenyl)-4-pyrimidinyl]benzenesulphon-amide, melting point 165-166°C.

The starting material was obtained from p-t-butylbenzenesulphonamide potassium and 4,6-dichloro-5-(p-methoxyphenyl)-pyrimidine, melting point 204-205°C.

Example 56

In analogy to Example 50, from 216 mg of rac-p-sec-butyl-N-[6-chloro-5-(p-methoxyphenyl)-4-pyrimidinyl]benzenesulphonamide there were obtained 135 mg of rac-p-sec-butyl-N-[6-(2-hydroxyethoxy)-5-(p-methoxyphenyl)-4-pyrimidinyl]-benzenesulphonamide, melting point 120-122°C.

The starting material was prepared from rac-p-sec-butylbenzenesulphonamide potassium and 2,6-dichloro-5-(p-methoxyphenyl)pyrimidine, melting point 172-173°C.

Example 57

In analogy to Example 50, from 280 mg of N-[6-chloro-5-[(p-methylthio)phenyl]-4-pyrimidinyl]-p-isopropylbenzenesulphonamide there were obtained 240 mg of N-[6-(2-hydroxyethoxy)-5-[p-(methylthio)phenyl]-4-pyrimidinyl]-p-isopropylbenzenesulphonamide, melting point 135-136°C (from diisopropyl ether).

The starting material was prepared as follows:

15.2 g of (p-methylthio)benzaldehyde were dissolved in 50 ml of isopropanol. 1.31 g of sodium borohydride in 150 ml of isopropanol were added dropwise to this solution within 0.5 hour while cooling in an ice bath. After stirring at room temperature for 1 hour 5 ml of acetone were added and the solvent was subsequently distilled off. The residue was partitioned between methylene chloride and water. After working-up there was obtained (p-methylthio)benzyl alcohol, melting point 40-41°C (from isopropanol).

7.71 g of (p-methylthio)benzyl alcohol were dissolved in 25 ml of dry methylene chloride. 4 ml of $SOCl_2$ were added to

this solution within 30 minutes while cooling in an ice bath. After distilling off the solvent and the excess reagent the residue was filtered over silica gel with methylene chloride. After distillation there were obtained 4.3 g of (p-methylthio)benzyl chloride, boiling point 92°C/0.05 Torr.

9 g of the benzyl chloride obtained in the preceding paragraph were added to a suspension of 10 g of potassium cyanide and 0.1 g of sodium iodide in 100 ml of dimethylformamide. The reaction mixture was stirred at 90°C for 1 hour with the exclusion of moisture. Thereafter, the dimethylformamide was distilled off and the residue was partitioned between toluene and water. Working-up of the organic phase yielded (p-methylthio)benzyl cyanide, melting point 28-30°C.

12 g of (p-methylthio)benzyl cyanide were dissolved in 30 ml of ethylene glycol and treated with 9 g of NaOH (as a 30% solution). The reaction mixture was stirred at 140°C for 3 hours. After cooling to room temperature the mixture was acidified with 25% hydrochloric acid, the precipitate was taken up in ethyl acetate and extracted with water. There were obtained 11.5 g of (p-methylthio)phenylacetic acid; melting point 94-96°C.

11 g of the previously obtained acid were dissolved in 50 ml of abs. ethanol and 25 ml of ethyl orthoformate and 1 g of methanesulphonic acid. The formate formed during the reaction was distilled off continuously. The reaction had finished after 4 hours. The acid catalyst was neutralized with the stoichiometric amount of sodium ethylate, the solvent was distilled off, the residue was taken up in methylene chloride and filtered over silica gel. There were obtained 12 g of ethyl (p-methylthio) phenylacetate, melting point 46-47°C.

The previously obtained compound was converted into diethyl (p-methylthio)phenylmalonate in analogy to the procedure described in Example 50. Boiling point 120°C/0.05 Torr.

5-(p-Methylthio)phenyl-6-hydroxy-4(3H)-pyrimidinone was obtained from the previously obtained diethyl malonate in analogy to the procedure described in Example 50.

The previously described pyrimidinone was converted with sodium methylate into the dialkoxy compound from which 4,6-dichloro-5-(p-methylthio)phenyl-pyrimidine was obtained by reaction with phosphorus oxychloride.

N-[6-Chloro-5-[p-(methylthio)phenyl[-4-pyrimidinyl]-p-isopropylbenzenesulphonamide, melting point 193-195°C, was obtained from the previously described 4,6-dichloro compound by reaction with p-isopropylbenzenesulphonamide potassium.

Example 58

In analogy to Example 50, from 230 mg of N-[6-chloro-5-[p-(methylthio)phenyl[-4-pyrimidinyl]-α,α,α-trifluoro-p-toluene-sulphonamide there were obtained 160 mg of N-[6-(2-hydroxy-ethoxy)-5-[p-(methylthio)phenyl]-4-pyrimidinyl]-α,α,α-trifluoro-p-toluenesulphonamide, melting point 266-268°C.

The starting material was obtained from 4,6-dichloro-5-p-(methylthio)phenyl-pyrimidine and α,α,α-trifluoro-p-toluene-sulphonamide potassium, melting point 250-252°C.

Example 59

300 mg of N-[6-chloro-5-(p-methoxybenzyl)-4-pyrimidinyl]-p-methoxybenzenesulphonamide were added to a sodium glycolate solution from 1 ml of dry ethylene glycol and 46 mg of sodium. The reaction mixture was heated at 125°C for 4 hours under an argon atmosphere. Thereafter, the ethylene glycol was distilled off under reduced pressure, the residue was partitioned between ethyl acetate and 1N hydrochloric acid, the organic phase was washed neutral, dried and evaporated. The residue was chromatographed on silica gel with methylene chloride/ethyl acetate (1:1 v/v). There were obtained 250 mg of

N-[6-(2-hydroxyethoxy)-5-(o-methoxybenzyl)-4-pyrimidinyl]-p-methoxybenzenesulphonamide, melting point 161-162°C.

The starting material was prepared as follows:

By Knoevenagel condensation of o-methoxybenzaldehyde with diethyl malonate there was obtained diethyl o-methoxybenzylidenemalonate, boiling point 140°C/0.05 Torr.

Hydrogenation of the previously obtained compound in ethanol in the presence of palladium/carbon yielded diethyl o-methoxybenzylmalonate, boiling point 115°C/0.01 Torr.

Reaction of diethyl o-methoxybenzylmalonate with formamidine hydrochloride yielded 5-(o-methoxybenzyl)-6-hydroxy-4(3H)-pyrimidinone from which, by reaction with phosphorus oxychloride, there was obtained 4,6-dichloro-5-(o-methoxybenzyl)pyrimidine, melting point 95-96°C.

Reaction of 4,6-dichloro-5-(o-methoxybenzyl)-4-pyrimidine and p-methoxybenzenesulphonamide potassium yielded N-[6-chloro-5-(o-methoxybenzyl)-4-pyrimidinyl]-p-methoxy-benzenesulphonamide, melting point 149-151°C.

Example 60

In analogy to Example 59, from N-[6-chloro-5-(o-chloro-benzyl)-4-pyrimidinyl]-p-toluenesulphonamide there was obtained N-[6-(2-hydroxyethoxy)-5-(o-chlorobenzyl)-4-pyrimidinyl]-p-toluenesulphonamide.

The starting material was prepared aas follows:

Diethyl malonate and o-chlorobenzyl chloride were converted into diethyl o-chlorobenzylmalonate, boiling point 115°C/0.55 Torr.

Condensation of diethyl o-chlorobenzylmalonate with formamidine yielded 5-(o-chlorobenzyl)-6-hydroxy-4(3H)-pyrimidinone which, by reaction with phosphorus oxychloride, yielded 4,6-chloro-5-(o-chlorobenzyl)pyrimidine, melting point 110-112°C.

From 4,6-dichloro-5-(o-chlorobenzyl)pyrimidine and p-toluenesulphonamide potassium there was obtained N-[6-chloro-5-(o-chlorobenzyl)-4-pyrimidinyl]-p-toluenesulphonamide which was used as the crude product.

Example 61

In analogy to Example 59, from N-[6-chloro-5-(o-methoxybenzyl)-4-pyrimidinyl]-p-(methylthio)benzenesulphonamide there was obtained N-[6-(2-hydroxyethoxy)-5-(o-methoxybenzyl)-4-pyrimidinyl]-p-(methylthio)benzenesulphonamide, melting point 134-136°C.

The starting material was prepared from 4,6-dichloro-5-(o-methoxybenzyl)pyrimidine and (p-methylthio)benzenesulphonamide potassium. Melting point 157-159°C.

Example 62

In analogy to Example 59, from N-[6-chloro-5-(o-methoxybenzyl)-4-pyrimidinyl]-α,α,α-trifluoro-p-toluenesulphonamide there was obtained N-[6-(2-hydroxyethoxy)-5-(o-methoxybenzyl)-4-pyrimidinyl]-α,α,α-trifluoro-p-toluenesulphonamide, melting point 133-134°C.

The starting material was obtained from 4,6-dichloro-5-(o-methoxybenzyl)pyrimidine and p-trifluoromethylbenzenesulphonamide potassium, melting point 163°C.

Example 63

In analogy to Example 59, from N-[6-chloro-5-(o-methoxybenzyl)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide there was obtained N-[6-(2-hydroxyethoxy)-5-(o-methoxybenzyl)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide, melting point 112-113°C.

The sodium salt, melting point 225°C, was prepared using sodium methylate in methanol.

The starting material was prepared from 4,6-dichloro-5-(o-methoxybenzyl)pyrimidine and isopropylbenzenesulphonamide potassium, melting point 138-139°C.

Example 64

In analogy to Example 59, from p-t-butyl-N-[6-chloro-5-(o-methoxybenzyl)-4-pyrimidinyl]benzenesulphonamide there was obtained p-t-butyl-N-[6-(2-hydroxyethoxy)-5-(o-methoxybenzyl)-4-pyrimidinyl]benzenesulphonamide, melting point 138-140°C (from diisopropyl ether).

The starting material was prepared from 4,6-dichloro-5-(o-methoxybenzyl)pyrimidine and p-t-butylbenzenesulphonamide potassium, melting point 215-216°C.

Example 65

In analogy to Example 59, from N-[6-chloro-5-(o-chlorobenzyl)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide there was obtained N-[6-(2-hydroxyethoxy)-5-(o-chlorobenzyl)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide.

The starting material was prepared from 4,6-dichloro-5-(o-chlorobenzyl)pyrimidine and p-isopropylbenzenesulphonamide potassium, melting point 166-167°C.

Example 66

In analogy to Example 59, from N-[6-chloro-5-(o-(methylthio)benzyl)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide there was obtained N-[6-(2-hydroxyethoxy)-5-(o-(methylthio)-benzyl)-4-pyrimidinyl]-p-isopropylbenzene-sulphonamide.

The starting material was prepared as follows:

By reacting thiosalicylic acid with dimethyl sulphate in the presence of tetrabutylammonium bromide there was obtained methyl 2-(methylthio)benzoate, melting point 64°C. Reduction with lithium alluminium hydride in dry tetrahydrofuran yielded 2-(methylthio)benzyl alcohol which was converted by reaction with $SOCl_2$ into 2-(methylthio)benzyl chloride, boiling point 90°C/0.3 Torr. Reaction of diethyl malonate with 2-(methylthio)benzyl chloride yielded diethyl 2-(methylthio)benzyl-malonate, boiling point 130°C/0.05 Torr. Condensation with formamidine yielded 5-[o-(methylthio)benzyl]-6-hydroxy-4(3H)-pyrimidinone which was converted into 4,6-dichloro-5-[o-(methylthio)benzyl]pyrimidine, melting point 91°C. From 4,6-dichloro-5-(o-(methylthio)benzyl)pyrimidine and p-isopropyl-benzenesuiphonamide potassium there was finally obtained N-[6-chloro-5-(o-(methylthio)benzyl)-4-pyrimidinyl]-p-isopropyl-benzenesulphonamide, melting point 145-146°C.

Example 67

In analogy to Example 59, from N-[6-chloro-5-(o-chlorobenzyl)-4-pyrimidinyl]-p-isobutylbenzenesulphonamide there was obtained N-[6-(2-hydroxyethoxy)-5-(o-chlorobenzyl)-4-pyrimidinyl]-p-isobutylbenzenesulphonamide, melting point 130-131°C.

The starting material was prepared from 4,6-dichloro-5-(o-chlorobenzyl)pyrimidine and p-isobutylbenzenesulphonamide potassium, melting point 147-149°C.

Example 69

In analogy to Example 50, from N-[6-chloro-5-(o-chlorobenzyl)-4-pyrimidinyl]-p-cyclohexylbenzenesulphonamide there was obtained N-[6-(2-hydroxyethoxy)-5-(o-chlorobenzyl)-4-pyrimidinyl]-p-cyclohexylbenzenesulphonamide, melting point 164-165°C.

The starting material was prepared from 4,6-dichloro-5-(o-chlorobenzyl)pyrimidine and p-cyclohexylbenzenesulphon- amide potassium, melting point 107-108°C.

Example 70

In analogy to Example 59, from N-[6-chloro-5-(o-chlorobenzyl)-4-pyrimidinyl]-p-isopentylbenzenesulphonamide there was obtained N-[6-(2-hydroxyethoxy)-5-(o-chlorobenzyl)-4-pyrimidinyl]-p-isopentylbenzenesulphonamide, melting point 127-128°C (from diisopropyl ether).

The starting material was prepared from 4,6-dichloro-5-(o-chlorobenzyl)pyrimidine and p-isopentylbenzenesulphonamide potassium, melting point 139-140°C.

Example 71

In analogy to Example 59, from N-[6-chloro-5-(o-methoxybenzyl)-4-pyrimidinyl]-p-(isopropylthio)benzenesulphonamide there was obtained N-[6-(2-hydroxyethoxy)-5-(o-methoxybenzyl)-4-pyrimidinyl]-p-(isopropylthio)benzenesulphonamide, melting point 127-128°C (from diisopropyl ether).

The starting material was prepared from 4,6-dichloro-5-(o-methoxybenzyl)pyrimidine and p-(isopropylthio)benzene-sulphonamide potassium.

Example 72

In analogy to Example 1, from p-chloro-N-[6-chloro-5-(p-chlorophenyl)-2-methyl-4-pyrimidinyl]benzenesuphonamide and ethylene glycol Na there was obtained p-chloro-N-[5-(p-chlorophenyl)-6-(2-hydroxyethoxy)-2-methyl-4-pyrimidinyl]benzenesulphonamide, melting point 163-164°C (from ether).

The starting material was prepared as follows:

From diethyl p-chlorophenylmalonate, acetamidine hydrochloride and sodium methylate there was prepared 5-(p-chlorophenyl)-2-methyl-4,6(1H,5H)-pyrimidinedione, melting point >270°C, and therefrom with $POCl_3$ there was prepared 4,6-dichloro-5-(p-chlorophenyl)-2-methylpyrimidine, melting point 181-183°C (from methylene chloride and isopropyl ether).

Reaction of this compound with p-chlorophenylsulphonamide yielded p-chloro-N-[6-chloro-5-(p-chlorophenyl)-2-methyl-4-pyrimidinyl]benzenesulphonamide, melting point 196-197°C (from acetonitrile).

Example 73

In analogy to Example 1, from p-chloro-N-[6-chloro-5-(p-nitrophenyl)-4-pyrimidinyl]benzenesulphonamide and p-chlorophenylsulphonamide there was obtained p-chloro-N-[6-(2-hydroxyethoxy)-5-(p-nitrophenyl)-4-pyrimidinyl]benzenesulphonamide, melting point 223-225°C (from methylene chloride and isopropyl ether).

The starting material was prepared as follows:

3.5 g of diethyl p-nitrophenylmalonate and 1.6 g of formamidine acetate were heated at 100°C for 3 hours. Thereafter, a further 3.2 g of formamidine acetate, 5 ml of abs. dimethylformamide and 1 ml of glacial acetic acid were added and the reaction mixture was heated at 110°C for 16 hours. After

evaporation of the solvent under reduced pressure, the residue was triturated with ether, filtered off under suction and taken up in a 1N NaOH solution. The solution was treated with some charcoal, filtered and adjusted to pH = 4.5 with glacial acetic acid. The precipitate was dried at 80°C under reduced pressure and thereafter taken up in 20 ml of $POCl_3$ and 1 ml of dimethylaniline and boiled at reflux while stirring. After evaporation of the solvent under reduced pressure the residue was taken up in ethyl acetate, the organic solution was washed with cold water, dried and evaporated. The residue was chromatographed on silica gel with cyclohexane-ether 9:1 and yielded 4,6-dichloro-5-(p-nitrophenyl)pyrimidine, melting point 159-161°C (from isopropyl ether).

Reaction of this compound with p-chlorophenylsulphonamide yielded p-chloro-N-[6-chloro-5-(p-nitrophenyl)-4-pyrimidinyl]- benzenesulphonamide, melting point 282-285°C (from acetonitrile).

Example 74

200 mg of p-chloro-N-[6-(2-hydroxyethoxy)-5-(p-nitrophenyl)-4-pyrimidinyl]benzenesulphonamide in 15 ml of glacial acetic acid and 2 ml of 4N HCl in dioxan were hydrogenated over 50 mg of palladium-carbon (10%) at room temperature and normal pressure. After filtering off the catalyst under suction the solution was evaporated under reduced pressure, the residue was dissolved in 30 ml of methanol and the solution was treated with 1 ml of dioxan-HCl. After 16 hours the solution was evaporated under reduced pressure and the residue was recrystallized from methanol and acetonitrile. There was obtained N-[5-(p-aminophenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]-p-chlorobenzenesulphonamide hydrochloride, melting point 206°C (with decomposition).

Example 75

In analogy to Example 1, from p-chloro-N-[5-(4-biphenylyl)-6-chloro-4-pyrimidinyl]benzenesulphonamide and ethylene glycol Na there was obtained N-[5-(4-biphenylyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]-p-chlorobenzenesulphonamide, melting point 213-214°C (from ethyl acetate).

The starting material was prepared as follows:

From diethyl 4-biphenylmalonate, formamidine acetate and sodium methylate there was obtained 5-(4-biphenylyl)-4,6(1H,5H)-pyrimidinedione, melting point >280°C, and therefrom with $POCl_3$ there was obtained 5-(4-biphenylyl)-4,6-dichloro-pyrimidine, melting point 144°C (from methylene chloride and n-hexane).

Reaction of this compound with p-chlorophenylsulphonamide yielded p-chloro-N-[5-(4-biphenylyl)-6-chloro-4-pyrimidinyl]-benzenesulphonamide, melting point 234-235°C (from acetonitrile).

Example 76

In analogy to Example 1, from p-chloro-N-[6-chloro-5-(α,α,α-trifluoro-p-tolyl)-4-pyrimidinyl]benzenesulphonamide and ethylene glycol Na there was obtained p-chloro-N-[(6-hydroxy-ethoxy)-5-(α,α,α-trifluoro-p-tolyl)-4-pyrimidinyl]benzene-sulphonamide, melting point 171-174°C (from acetone and isopropyl ether).

The starting material was prepared as follows:

From α,α,α-trifluoro-p-tolyl malonate and formamidine acetate there was obtained 5-α,α,α-trifluoro-p-tolyl)-4,6(1H,5H)-pyrimidinedione, melting point >280°C, and therefrom with $POCl_3$ there was obtained 4,6-dichloro-5-(α,α,α-p-tolyl)-pyrimidine, melting point 94-95°C (from n-hexane).

Reaction of this compound with p-chlorophenylsulphonamide yielded p-chloro-N-(6-chloro-5-(α,α,α-trifluoro-p-tolyl)-4-pyrimidinyl]benzenesulphonamide, melting point 262-264°C (from acetonitrile).

Example 77

In analogy to Example 27, from N-[5-[p-(benzyloxy)phenyl]-6-(2-hydroxyethoxy)-4-pyrimidinyl]-p-chlorobenzenesuphonamide there was obtained p-chloro-N-[5-(p-hydroxy-phenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]benzenesulphonamide, melting point 207-209°C (from acetonitrile and isopropyl ether).

Example 78

In analogy to Example 1, from N-[5-[p-(benzyloxy)phenyl]-6-chloro-4-pyrimidinyl]-p-chlorobenzenesulphonamide and ethylene glycol Na there was obtained N-[5-[p-(benzyloxy)phenyl]-6-(2-hydroxyethoxy)-4-pyrimidinyl]-p-chlorobenzenesulphonamide, melting point 160-161°C (from ether).

The starting material was prepared as follows:

From diethyl [p-(benzyloxy)phenyl]malonate and formamidine acetate there was obtained 5-[p-(benzyloxy)phenyl]-4,6(1H,5H)-dione, >280°C, and therefrom with $POCl_3$ there was obtained 5-[p-(benzyloxy)phenyl]-4,6-dichloropyrimidine, melting point 115-116°C (from methylene chloride and isopropyl ether). Reaction of this compound with p-chlorophenylsulphonamide yielded N-[5-[p-(benzyloxy)phenyl]-6-chloro-4-pyrimidinyl]-p-chlorobenzenesulphonamide, melting point 234-236°C (from ethyl acetate).

Example 79

In analogy to Example 1, from N-(6-chloro-4-(α,α,α-trifluoro-p-tolyl)-4-pyrimidinyl]-α,α,α-trifluoro-p-toluene-

sulphonamide and ethylene glycol Na there was obtained N-[6-(2-hydroxyethoxy)-5-(α,α,α-trifluoro-p-tolyl)-4-pyrimidinyl]-α,α,α-trifluoro-p-toluenesulphonamide, melting point 165-166°C (from methylene chloride and isopropyl ether).

The starting material was prepared from 4,6-dichloro-5-α,α,α-p-tolyl)-pyrimidine and α,α,α-trifluoro-p-tolylsulphonamide, melting point >270°C (from acetonitrile).

Example 80

In analogy to Example 1, from p-chloro-N-[6-chloro-5-(2-naphthylmethyl)-4-pyrimidinyl]benzenesulphonamide and ethylene glycol Na there was obtained p-chloro-N-[6-(2-hydroxyethoxy)-5-(2-naphthylmethyl)-4-pyrimidinyl]benzenesulphonamide, melting point 161°C (from acetonitrile and isopropyl ether).

The starting material was prepared as follows:

From diethyl (2-naphthylmethyl)malonate and formamidine acetate there was obtained 5-(2-naphthylmethyl)-4,6(1H,5H)-pyrimidinedione, melting point >270°C, and therefrom with $POCl_3$ there was obtained 4,6-dichloro-5-(2-naphthylmethyl)-pyrimidine, melting point 161-162°C (from methylene chloride and isopropyl ether).

Reaction of this compound with p-chlorophenylsulphonamide yielded p-chloro-N-[6-chloro-5-(2-naphthylmethyl)-4-pyrimidinyl]benzenesulphonamide, melting point 197-199°C (from acetonitrile).

Example 81

In analogy to Example 1, from N-[5-(p-bromophenyl)-6-chloro-4-pyrimidinyl]-p-isopropylbenzenesulphonamide and ethylene glycol Na there was obtained N-[5-(p-bromophenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]-p-isopropylbenzene-

sulphonamide, melting point 207-208°C (from acetonitrile and isopropyl ether).

The starting material was prepared from 5-(p-bromophenyl)-4,6-dichloropyrimidine and p-isopropylbenzenesulphonamide, melting point 271-273°C (from acetonitrile).

Example 82

In analogy to Example 1, from N-[6-chloro-5-(p-chlorophenyl)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide and ethylene glycol Na there was obtained N-[5-(p-chlorophenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide, melting point 162-164°C (from acetonitrile and isopropyl ether).

The starting material was prepared from 4,6-dichloro-5-(p-chlorophenyl)pyrimidine and p-isopropylbenzenesulphonamide, melting point 266-268°C (from acetonitrile).

Example 83

In analogy to Example 1, from N-(6-chloro-5-p-tolyl-4-pyrimidinyl)-p-isopropylbenzenesulphonamide and ethylene glycol Na there was obtained N-[6-hydroxyethoxy)-5-p-tolyl-4-pyrimidinyl]-p-isopropylbenzenesulphonamide, melting point 142-144°C (from isopropyl ether).

With sodium methylate there was obtained therefrom the Na salt, amorphous substance.

The starting material, N-(6-chloro-5-p-tolyl-4-pyrimidinyl)-p-isopropylbenzenesulphonamide, melting point 211-213°C (from acetonitrile), was prepared from 4,6-dichloro-5-p-tolylpyrimidine and p-isopropylbenzenesulphonamide.

Example 84

In analogy to Example 1, from p-tert-butyl-N-(6-chloro-5-p-tolyl-4-pyrimidinyl)benzenesulphonamide and ethylene glycol Na there was obtained p-tert-butyl-N-[6-(2-hydroxyethoxy)-5-p-tolyl-4-pyrimidinyl]benzenesulphonamide, melting point 169-170°C (from isopropyl ether) and therefrom with sodium methylate there was obtained the amorphous Na salt.

The starting material was prepared from 4,6-dichloro-5-p-tolylpyrimidine and p-tert-butylbenzenesulphonamide, melting point 222-224°C (from acetonitrile).

Example 85

In analogy to Example 1, from N-(6-chloro-5-p-tolyl-4-pyrimidinyl)-p-(2-methoxyethoxy)benzenesulphonamide and ethylene glycol Na there was obtained N-[6-(2-hydroxyethoxy)-5-p-tolyl-4-pyrimidinyl]-p-(2-methoxyethoxy)benzenesulphonamide, melting point 155-156°C (from isopropyl ether).

The starting material was prepared from 4,6-dichloro-5-p-tolylpyrimidine and p-(2-methoxyethoxy)benzenesulphonamide, melting point 172-173°C (from methylene chloride and isopropyl ether).

Example 86

In analogy to Example 1, from N-(6-chloro-5-p-tolyl-4-pyrimidinyl)-p-(trifluoromethoxy)benzenesulphonamide and ethylene glycol Na there was obtained N-[6-(2-hydroxyethoxy)-5-p-tolyl-4-pyrimidinyl]-p-(trifluoromethoxy)benzenesulphonamide, melting point 147-148°C (from isopropyl ether).

The starting material was prepared from 4,6-dichloro-5-p-tolylpyrimidine and p-(trifluoromethoxy)benzenesulphonamide, melting point 205-206°C (from acetonitrile and isopropyl ether).

Example 87

In analogy to Example 1, from p-butyl-N-(6-chloro-5-p-tolyl-4-pyrimidinyl)benzenesulphonamide and ethylene glycol Na there was obtained p-butyl-N-[6-(2-hydroxyethoxy)-5-p-tolyl-4-pyrimidinyl]benzenesulphonamide, melting point 136-137°C (from isopropyl ether).

The starting material was prepared from 4,6-dichloro-5-p-tolylpyrimidine and p-butylbenzenesulphonamide, melting point 168-169°C (from acetonitrile and isopropyl ether).

Example 88

In analogy to Example 1, from N-(6-chloro-5-p-tolyl-4-pyrimidinyl)-2-naphthalenesulphonamide and ethylene glycol Na there was obtained N-[6-(2-hydroxyethoxy)-5-p-tolyl-4-pyrimidinyl]-2-naphthalenesulphonamide, melting point 161-162°C (from acetone and isopropyl ether).

The starting material was prepared from 4,6-dichloro-5-p-tolylpyrimidine and 2-naphthalenesulphonamide, melting point 198-202°C (from acetonitrile).

Example 89

In analogy to Example 1, from N-(6-chloro-5-p-tolyl-4-pyrimidinyl)-p-toluenesulphonamide and ethylene glycol Na there was obtained N-[6-(2-hydroxyethoxy)-5-p-tolyl-4-pyrimidinyl]-p-toluenesulphonamide, melting point 169-170°C (from acetone and isopropyl ether).

The starting material was prepared from 4,6-dichloro-5-p-tolylpyrimidine and p-toluenesulphonamide, melting point 213-214°C (from acetonitrile and isopropyl ether).

Example 90

In analogy to Example 1, from N-(6-chloro-5-p-tolyl-4-pyrimidinyl)-α,α,α-trifluoro-p-toluenesulphonamide and ethylene glycol Na there was obtained N-[6-(2-hydroxyethoxy)-5-p-tolyl-4-pyrimidinyl]-α,α,α-trifluoro-p-toluenesulphonamide, melting point 162-163°C (from acetonitrile and isopropyl ether).

The starting material was prepared from 4,6-dichloro-5-p-tolylpyrimidine and α,α,α-trifluoro-p-toluenesulphonamide, melting point 231-233°C (from acetonitrile).

Example 91

In analogy to Example 1, from N-(6-chloro-5-p-tolyl-4-pyrimidinyl)-p-fluorobenzenesulphonamide and ethylene glycol Na there were obtained, after chromatography, p-fluoro-N-[6-(2-hydroxyethoxy)-5-p-tolyl-4-pyrimidinyl]benzenesulphonamide, melting point 167-169°C (from acetone and isopropyl ether), and p-(2-hydroxyethoxy)-N-[6-(2-hydroxyethoxy)-5-p-tolyl-4-pyrimidinyl]benzenesulphonamide, melting point 174-176°C (from acetone and isopropyl ether).

The starting material was prepared from 4,6-dichloro-5-p-tolylpyrimidine and p-fluorobenzenesulphonamide, melting point 207-208°C (from acetonitrile and isopropyl ether).

Example 92

In analogy to Example 1, from N-(6-chloro-5-p-tolyl-4-pyrimidinyl)-p-propylbenzenesulphonamide and ethylene glycol Na there was obtained N-[6-(2-hydroxyethoxy)-5-p-tolyl-4-pyrimidinyl]-p-propylbenzenesulphonamide, melting point 152-153°C (from isopropyl ether)

The starting material was prepared from 4,6-dichloro-5-p-tolylpyrimidine and p-propylbenzenesulphonamide, melting point 171-172°C (from acetonitrile).

Example 93

In analogy to Example 1, from N-(6-chloro-5-p-tolyl-4-pyrimidinyl)-o-propylbenzenesulphonamide and ethylene glycol Na there was obtained N-[6-(2-hydroxyethoxy)-5-p-tolyl-4-pyrimidinyl]-o-propylbenzenesulphonamide, melting point 195-196°C (from methylene chloride and isopropyl ether).

The starting material was prepared from 4,6-dichloro-5-p-tolylpyrimidine and o-propylbenzenesulphonamide, melting point 150-151°C (from isopropyl ether).

Example 94

In analogy to Example 1, from N-(6-chloro-5-p-tolyl-4-pyrimidinyl)-p-ethylbenzenesulphonamide and ethylene glycol Na there was obtained p-ethyl-N-[6-(2-hydroxyethoxy)-5-p-tolyl-4-pyrimidinyl]benzenesulphonamide, melting point 138-139°C (from methylene chloride and isopropyl ether).

The starting material was prepared from 4,6-dichloro-5-p-tolylpyrimidine and p-ethylbenzenesulphonamide, melting point 180-181°C (from acetonitrile).

Example 95

In analogy to Example 1, from N-(6-chloro-5-p-tolyl-4-pyrimidinyl)-o-ethylbenzenesulphonamide and ethylene glycol Na there was obtained o-ethyl-N-[6-(2-hydroxyethoxy)-5-p-tolyl-4-pyrimidinyl]benzenesulphonamide, melting point 136-138°C (from acetone and isopropyl ether).

The starting material was prepared from 4,6-dichloro-5-p-tolylpyrimidine and o-ethylbenzenesulphonamide, melting point 159-160°C (from acetonitrile and isopropyl ether).

Example 96

In analogy to Example 1, from N-(6-chloro-5-p-tolyl-4-pyrimidinyl)-p-cyclopentylbenzenesulphonamide and ethylene glycol Na there was obtained p-cyclopentyl-N-[6-(2-hydroxy-ethoxy)-5-p-tolyl]benzenesulphonamide, melting point 179-181°C (from acetone and isopropyl ether).

The starting material was prepared from 4,6-dichloro-5-p-tolylpyrimidine and p-cyclopentylbenzenesulphonamide, melting point 192-194°C (from acetonitrile and isopropyl ether).

Example 97

In analogy to Example 1, from N-(6-chloro-5-p-tolyl-4-pyrimidinyl)-α,α,α-trifluoro-o-toluenesulphonamide and ethylene glycol Na there was obtained α,α,α-trifluoro-N-[6-(2-hydroxy-ethoxy)-5-p-tolyl-4-pyrimidinyl]-o-toluenesulphonamide, melting point 166-167°C (from methylene chloride and isopropyl ether).

The starting material was prepared from 4,6-dichloro-5-p-tolylpyrimidine and α,α,α-trifluoro-o-toluenesulphonamide, melting point 129-131°C (from methylene chloride and isopropyl ether).

Example 98

In analogy to Example 1, from N-(6-chloro-5-p-tolyl-4-pyrimidinyl)-o-toluenesulphonamide and ethylene glycol Na there was obtained N-[6-(2-hydroxyethoxy)-5-p-tolyl-4-pyrimidinyl]-o-toluenesulphonamide, melting point 149-150°C (from ethyl acetate and isopropyl ether).

The starting material was prepared from 4,6-dichloro-5-p-tolylpyrimidine and o-toluenesulphonamide, melting point 198-199°C (from acetonitrile).

Example 99

In analogy to Example 1, from N-(6-chloro-5-p-tolyl-4-pyrimidinyl)-2,4-xylenesulphonamide and ethylene glycol Na there was obtained N-[6-(2-hydroxyethoxy)-5-p-tolyl-4-pyrimidinyl]-2,4-xylenesulphonamide, melting point 158-159°C (from isopropyl ether).

The starting material was prepared from 4,6-dichloro-5-p-tolylpyrimidine and 2,4-xylenesulphonamide, melting point 233°C (from acetonitrile and isopropyl ether).

Example 100

In analogy to Example 1, from p-chloro-N-[6-chloro-5-(1-naphthylmethyl)-4-pyrimidinyl]benzenesulphonamide and ethylene glycol Na there was obtained p-chloro-N-[6-(2-hydroxyethoxy)-5-(1-naphthylmethyl)-4-pyrimidinyl]benzenesulphonamide, melting point 204-205°C (from acetonitrile and isopropyl ether).

The starting material was prepared as follows:

From diethyl 1-naphthylmalonate and formamidine acetate there was obtained 5-(1-naphthylmethyl)-4,6(1H,5H)-pyrimidinedione, melting point >270°C, and therefrom, after drying under reduced pressure at 80°C, by reaction with $POCl_3$ there was obtained 4,6-dichloro-5-(1-naphthylmethyl)-pyrimidine, melting point 111-112°C (from methylene chloride and isopropyl ether).

Reaction of this compound with p-chlorophenylsulphonamide yielded p-chloro-N-[6-chloro-5-(1-naphthylmethyl)-4-pyrimidinyl]benzenesulphonamide, melting point 202-203°C (from acetonitrile).

Example 101

In analogy to Example 1, from N-[6-chloro-5-(p-isopropylphenyl)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide and ethylene glycol Na there was obtained N-6-(2-hydroxyethoxy)-5-(p-isopropylphenyl)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide, melting point 142-144°C (from isopropyl ether).

The starting material was prepared as follows:

From diethyl (p-isopropylphenyl)malonate and formamidine acetate there was obtained 5-(p-isopropylphenyl)-4,6(1H,5H)-pyrimidinedione, melting point >290°C, and therefrom by reaction with $POCl_3$ there was obtained 4,6-dichloro-5-(p-isopropylphenyl)pyrimidine, melting point 69-70°C (from n-hexane). Reaction of this compound with p-isopropylbenzenesulphonamide yielded N-[6-chloro-5-(p-isopropylphenyl)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide, melting point 198-199°C (from acetonitrile and isopropyl ether).

Example 102

In analogy to Example 1, from N-[6-chloro-5-(p-isopropylphenyl)-4-pyrimidinyl]-p-cyclopentylbenzene-sulphonamide and ethylene glycol Na there was obtained p-cyclopentyl-N-[6-(2-hydroxyethoxy)-5-(p-isopropylphenyl)-4-pyrimidinyl]benzenesulphonamide, melting point 132°C (decomposition) (from acetone-isopropyl ether).

The starting material was prepared from 4,6-dichloro-5-(p-isopropylphenyl)pyrimidine and p-cyclopentylbenzenesulphonamide, melting point 183-189°C (from methylene chloride and isopropyl ether).

Example 103

By heating of p-t-butyl-N-[6-chloro-5-(o-methoxybenzyl)-4-pyrimidinyl]benzenesulphonamide and pyridine-2-carboxylic

acid in methylene chloride in the presence of dicyclohexylcarbodiimide there is obtained 4-t-butyl-N-[6-[2-(pyridin-2-ylcarbonyloxy)ethoxy]-5-(2-methoxybenzyl)pyrimidin-4-yl]-benzenesulphonamide.

In analogous manner there can be obtained

4-t-butyl-N-[6-[2-(pyridin-3-ylcarbonyloxy)ethoxy]-5-(2-methoxybenzyl)pyrimidin-4-yl]benzenesulphonamide;

4-t-butyl-N-[6-[2-(pyridin-4-ylcarbonyloxy)ethoxy]-5-(2-methoxybenzyl)pyrimidin-4-yl]benzenesulphonamide;

4-t-butyl-N-[6-[2-[(3-methylisoxazol-5-yl)carbonyloxy]-ethoxy]-5-(2-methoxybenzyl)pyrimidin-4-yl]benzenesulphonamide;

4-t-butyl-N-[6-[2-(furan-2-ylcarbonyloxy)ethoxy]-5-(2-methoxybenzyl)pyrimidin-4-yl]benzenesulphonamide;

4-t-butyl-N-[6-[2-(furan-3-ylcarbonyloxy)ethoxy]-5-(2-methoxybenzyl)pyrimidin-4-yl]benzenesulphonamide;

4-t-butyl-N-[6-[2-(thiophen-2-ylcarbonyl)ethoxy]-5-(2-methoxybenzyl)pyrimidin-4-yl]benzenesulphonamide;

4-t-butyl-N-[6-[2-(thiophen-3-ylcarbonyl)ethoxy]-5-(2-methoxybenzyl)pyrimidin-4-yl]benzenesulphonamide.

Example A

Tablets containing the following ingredients can be produced in a conventional manner:

Ingredients	Per tablet
Compound of formula I	10.0 - 100.0 mg
Lactose	125.0 mg
Corn starch	75.0 mg
Talc	4.0 mg
Magnesium stearate	1.0 mg

Example B

Capsules containing the following ingredients can be produced in a conventional manner:

Ingredients	Per tablet
Compound of formula I	25.0 mg
Lactose	150.0 mg
Corn starch	20.0 mg
Talc	5.0 mg

Example C

Injection solutions can have the following composition:

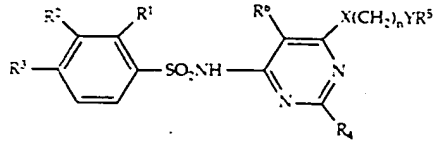
Compound of formula I		3.0 mg
Gelatine		150.0 mg
Phenol		4.7 mg
Water for injection solutions	ad	1.0 mg

Example D

500 mg of compound of formula I are suspended in 3.5 ml of Myglyol 812 and 0.08 g of benzyl alcohol. This suspension is filled into a container having a dosage valve. 5.0 g of Freon 12 are filled into the container through the valve. The Freon is dissolved in the Myglyol-benzyl alcohol mixture by shaking. This spray container contains about 100 single doses which can be administered individually.

Claims

1. The use of compounds of the formula



I

wherein

R^1 signifies hydrogen, lower-alkyl, lower-alkoxy, lower-alkylthio, halogen or trifluoromethyl;

R^2 signifies hydrogen, halogen, lower-alkoxy, hydroxy-lower-alkoxy or trifluoromethyl; and

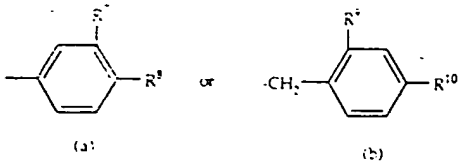
R^3 signifies hydrogen, hydroxy, halogen, alkylthio, cycloalkyl, hydroxy-lower-alkyl, hydroxy-lower-alkoxy, hydroximino-lower-alkyl, lower-alkenyl, oxo-lower-alkyl, trifluoromethyl, trifluormethoxy, lower-alkoxy, lower-alkoxy-lower-alkoxy or aryl-lower-alkoxy; or

R^2 and R^3 together signify butadienyl;

R^4 signifies hydrogen, lower-alkyl, aryl or heteroaryl;

R^5 signifies hydrogen, lower-alkanoyl, benzoyl, heterocyclyl-carbonyl or tetrahydropyran-2-yl;

R^6 signifies a residue of the formula



(a) (b)

R^7 signifies hydrogen, lower-alkoxy or nitro; and

R^8 signifies hydrogen, halogen, lower-alkyl, lower-alkoxy, lower-alkylthio, nitro, hydroxy, amino or trifluoromethyl; or

R^7 and R^8 together signify butadienyl;

R^9 signifies hydrogen, halogen, lower-alkyl, lower-alkoxy, lower-alkylthio or trifluoromethyl;

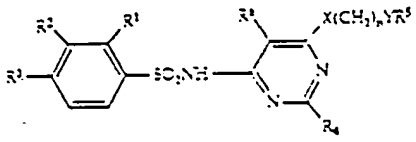
R^{10} signifies hydrogen, halogen, lower-alkyl, lower-alkoxy or lower-alkylthio;

X and Y each independently signify O, S or NH; and

n signifies 2, 3 or 4;

and salts thereof as active ingredients for the manufacture of medicaments for the treatment of circulatory disorders, especially hypertension, ischemia, vasospasms and angina pectoris.

2. Compounds of the formula



wherein

R^1 signifies hydrogen, lower-alkyl, lower-alkoxy, lower-alkylthio, halogen or trifluoromethyl;

R^2 signifies hydrogen, halogen, lower-alkoxy, hydroxy-lower-alkoxy or trifluoromethyl; and

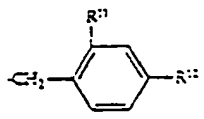
R^3 signifies hydrogen, hydroxy, halogen, alkylthio, cycloalkyl, hydroxy-lower-alkyl, hydroxy-lower-alkoxy, hydroximino-lower-alkyl, lower-alkenyl, oxo-lower-alkyl, trifluoromethyl, trifluormethoxy, lower-alkoxy, lower-alkoxy-lower-alkoxy or aryl-lower-alkoxy; or

R^2 and R^3 together signify butadienyl;

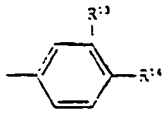
R^4 signifies hydrogen, lower-alkyl, aryl or heteroaryl;

R^5 signifies hydrogen, lower-alkanoyl, benzoyl, heterocyclyl-carbonyl or tetrahydropyran-2-yl;

R^6 signifies a residue of the formula



(c)



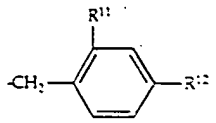
(d)

R^{11} signifies halogen, lower-alkoxy, lower-alkylthio or trifluoromethyl; R^{12} signifies hydrogen or lower-alkoxy; R^{13} signifies hydrogen, lower-alkoxy or nitro; R^{14} signifies hydrogen, halogen, lower-alkyl, lower-alkoxy, lower-alkylthio or nitro or R^{13} and R^{14} together signify butadienyl;

X and Y each independently signify O, S or NH; and

n signifies 2, 3 or 4.

3. Compounds as in claim 2 wherein R^6 represents a residue of the formula



(c)

R^1-R^5, R^{11}, R^{12}, X and Y and n have the significance given in claim 2.

4. Compounds as in claim 3 in which R^4 is hydrogen, lower-alkyl or aryl and the remaining symbols have the significance given in claim 2.

5. The compounds

N-[5-(2,6-dimethoxybenzyl)-6-(3-hydroxypropyl)-4-pyrimidinyl]-p-vinylbenzenesulphonamide,

α,α,α-trifluoro-N-[6-(2-hydroxyethoxy)-6-[o-(trifluoromethyl)benzyl]pyrimidinyl]-p-toluenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-[o-(trifluoromethyl)benzyl]-4-

pyrimidinyl]-p-methoxybenzenesulphonamide,

p-chloro-N-[6-(2-hydroxyethoxy)-5-[o-(trifluoromethyl)-benzyl]-4-pyrimidinyl]benzenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-(o-methoxybenzyl)-4-pyrimidinyl]-p-vinylbenzenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-[o-(trifluoromethyl)benzyl]-4-pyrimidinyl]-p-(methylthio)benzenesulphonamide,

N-[5-(2,4-dimethoxybenzyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide,

rac-N-[5-(o-methoxybenzyl)-6-[2-[(tetrahydro-2H-pyran-2-yl)oxy]ethoxy]-4-pyrimidinyl]-p-vinylbenzenesulphonamide,

rac-p-[[5-(o-methoxybenzyl)-6-[2-[(tetrahydro-2H-pyran-2-yl)oxy]ethoxy]-4-pyrimidinyl]sulphamoyl]benzaldehyde,

p-[(RS)-1-hydroxyethyl]-N-[5-(-methoxybenzyl)-6-[2-[[(RS)-tetrahydro-2H-pyran-2-yl]oxy]ethoxy]-4-pyrimidinyl]-benzenesulphonamide,

rac-α-hydroxy-N-[5-(o-methoxybenzyl)-6-[2-[(tetrahydro-2H-pyran-2-yl)oxy]ethoxy]-4-pyrimidinyl]-p-toluene-sulphonamide,

rac-α-[(>E/Z)-hydroxyimino-N-[5-(o-methoxybenzyl)-6-[2-[(tetrahydro-2H-pyran-2-yl)oxy]ethoxy]-4-pyrimidinyl]-p-toluenesulphonamide,

rac-N-6-(2-hydroxyethoxy)-5-(o-methoxybenzyl)-p-(1-hydroxyethyl)benzenesulphonamide,

α-[(E/Z)-hydroxyimino]-N-[6-(2-hydroxyethoxy)-5-(o-methoxybenzyl)-4-pyrimidinyl]-p-toluenesulphonamide,

p-[[6-(2-hydroxyethoxy)-5-(o-methoxybenzyl)-4-pyrimidinyl]sulphamoyl]benzaldehyde,

2-[[5-(o-methoxybenzyl)-6-[(p-vinylphenyl)sulphamoyl]-4-pyrimidinyl]oxy]ethyl acetate,

N-[6-(2-hydroxyethoxy)-5-(o-methoxybenzyl)-4-pyrimidinyl]-p-methoxybenzenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-(o-chlorobenzyl)-4-pyrimidinyl]-p-toluenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-(o-methoxybenzyl)-4-pyrimidinyl]-p-methylthiobenzenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-(o-methoxybenzyl)-4-pyrimidinyl]-α,α,α-trifluoro-p-toluenesulphonamide.

N-[6-(2-hydroxyethoxy)-5-(o-methoxybenzyl)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide,

p-t-butyl-N-[6-(2-hydroxyethoxy)-5-(o-methoxybenzyl)-4-pyrimidinyl]benzenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-(o-chlorobenzyl)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-(o-methylthiobenzyl)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide,

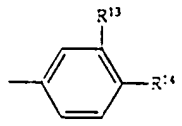
N-[6-(2-hydroxyethoxy)-5-(o-chlorobenzyl)-4-pyrimidinyl]-p-isobutylbenzenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-(o-chlorobenzyl)-4-pyrimidinyl]-p-cyclohexylbenzenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-(o-chlorobenzyl)-4-pyrimidinyl]-p-isopentylbenzenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-(o-methoxybenzyl)-4-pyrimidinyl]-p-isopropylthiobenzenesulphonamide.

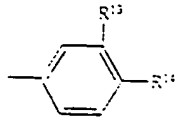
6. Compounds as in claim 2 wherein R^6 represents a residue of the formula



(d)

R^1-R^5, R^{13}, R^{14}, X, Y, and n have the significance given in claim 2.

7. Compounds as in claim 2 wherein R^9 represents a residue of the formula



(d)

R^1-R^4, R^5, R^{13}, R^{14}, X, Y and n have the significance given in claim 2, and R^7 is hydrogen, lower-alkyl or aryl.

8. The compounds

N-[5-(p-chlorophenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]-α,α,α-trifluoro-p-toluenesulphonamide,

N-[5-(p-chlorophenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]-p-(trifluoromethoxy)benzenesulphonamide,

p-chloro-N-[5-(m-chlorophenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]benzenesulphonamide,

p-chloro-N-[5-(p-fluorophenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]benzenesulphonamide,

N-[5-(p-chlorophenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]-p-fluorobenzenesulphonamide,

o-chloro-N-[5-(p-chlorophenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]benzenesulphonamide,

p-chloro-N-[5-(3,4-dimethoxyphenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]benzenesulphonamide,

3,4-dichloro-N-[5-(p-chlorophenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]benzenesulphonamide,

N-5-(p-chlorophenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]-α,α,α-α',α',α'-hexafluoro-3,5-xylenesulphonamide,

3-chloro-N-[5-(p-chlorophenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]-4-(2-hydroxyethoxy)benzenesulphonamide,

p-chloro-N-(6-(2-hydroxyethoxy)-5-(p-nitrophenyl)-4-pyrimidinyl]benzenesulphonamide,

p-butoxy-N-[5-(p-chlorophenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]benzenesulphonamide,

N-[5-(p-chlorophenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]-3,4-dimethoxybenzenesulphonamide,

2-chloro-N-[5-(p-chlorophenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]-α,α,α-trifluoro-p-toluenesulphonamide,

6-chloro-N-[5-(p-chlorophenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]-α,α,α-trifluoro-m-toluenesulphonamide,

2,3,4-trichloro-N-[(5-chlorophenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]benzenesulphonamide,

m-chloro-N-(p-chlorophenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]benzenesulphonamide,

2,4-dichloro-N-[5-(p-chlorophenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]benzenesulphonamide,

N-5-(p-chlorophenyl)-6-(2-hydroxyethoxy)-α,α,α-trifluoro-m-toluenesulphonamide,

N-5-(p-chlorophenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]-α,α,α-trifluoro-o-toluenesulphonamide,

N-[5-(p-chlorophenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]-2-naphthalenesulphonamide,

p-chloro-N-[6-(2-hydroxyethoxy)-5-(m-nitrophenyl)-4-pyrimidinyl]benzenesulphonamide,

α,α,α-trifluoro-N-[6-(2-hydroxyethoxy)-5-(m-nitrophenyl)-4-pyrimidinyl]-p-toluenesulphonamide,

p-(benzyloxy)-N-[5-(p-chlorophenyl)-6-(2-hydroxyethoxy)4-pyrimidinyl]benzenesulphonamide,

N-[5-(p-chlorophenyl)-4-pyrimidinyl]-p-hydroxybenzenesulphonamide,

N-[5-(p-chlorophenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]-p-(2-methoxyethoxy)benzenesulphonamide,

N-[5-(p-bromophenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]-p-chlorobenzenesulphonamide,

p-chloro-N-[6-(2-hydroxyethoxy)-5-p-tolyl-4-pyrimidinyl]benzenesulphonamide,

N-[5-(p-chlorophenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]-α,α,α-trifluoro-p-toluenesulphonamide sodium salt,

N-[6-(2-hydroxyethoxy)-5-(p-methoxyphenyl)-4-pyrimidinyl]-p-toluenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-(p-methoxyphenyl)-4-pyrimidinyl]-p-methoxybenzenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-(p-methoxyphenyl)-4-pyrimidinyl]-p-(methylthio)benzenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-(p-methoxyphenyl)-2-methyl-4-pyrimidinyl]-p-methoxybenzenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-(p-methoxyphenyl)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide,

p-t-butyl-N-[6-(2-hydroxyethoxy)-5-(p-methoxyphenyl)-4-pyrimidinyl]benzenesulphonamide,

rac-p-sec-butyl-N-[6-(2-hydroxyethoxy)-5-(p-methoxyphenyl)-4-pyrimidinyl]benzenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-[p-(methylthio)phenyl]-4-pyrimidinyl]-p-isopropylbenzenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-[p-(methylthio)phenyl]-4-pyrimidinyl]-α,α,α-trifluoro-p-toluenesulphonamide,

p-chloro-N-[5-(p-chlorophenyl)-6-(2-hydroxyethoxy)-2-methyl-4-pyrimidinyl]benzenesulphonamide,

p-chloro-N-[6-(2-hydroxyethoxy)-5-(p-nitrophenyl)-4-pyrimidinyl]benzenesulphonamide,

N-[5-(p-aminophenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]-p-chlorobenzenesulphonamide hydrochloride,

N-[5-(4-biphenylyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]-p-chlorobenzenesulphonamide,

p-chloro-N-[(6-hydroxyethoxy)-5-(α,α,α-trifluoro-p-tolyl)-4-pyrimidinyl]benzenesulphonamide,

p-chloro-N-[5-(p-hydroxyphenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]benzenesulphonamide,

N-[5-[p-(benzyloxy)phenyl]-6-(2-hydroxyethoxy)-4-pyrimidinyl]-p-chlorobenzenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-(α,α,α-trifluoro-p-tolyl)-4-pyrimidinyl]-α,α,α-trifluoro-p-toluenesulphonamide,

N-[5-(p-chlorophenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide,

N-[6-hydroxyethoxy)-5-p-tolyl-4-pyrimidinyl]-p-isopropyl-benzenesulphonamide,

p-tert-butyl-N-[6-(2-hydroxyethoxy)-5-p-tolyl-4-pyrimidinyl]benzenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-p-tolyl-4-pyrimidinyl]-p-(2-methoxyethoxy)benzenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-p-tolyl-4-pyrimidinyl]-p-(trifluoromethoxy)benzenesulphonamide,

p-butyl-N-[6-(2-hydroxyethoxy)-5-p-tolyl-4-pyrimidinyl]-benzenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-p-tolyl-4-pyrimidinyl]-2-naphthalenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-p-tolyl-4-pyrimidinyl]-p-toluenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-p-tolyl-4-pyrimidinyl]-α,α,α-trifluoro-p-toluenesulphonamide,

p-(2-hydroxyethoxy)-N-[6-(2-hydroxyethoxy)-5-p-tolyl-4-pyrimidinyl]benzenesulphonamide.

N-[6-(2-hydroxyethoxy)-5-p-tolyl-4-pyrimidinyl]-p-propylbenzenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-p-tolyl-4-pyrimidinyl]-o-propylbenzenesulphonamide,

p-ethyl-N-[6-(2-hydroxyethoxy)-5-p-tolyl-4-pyrimidinyl]-benzenesulphonamide,

o-ethyl-N-[6-(2-hydroxyethoxy)-5-p-tolyl-4-pyrimidinyl]-benzenesulphonamide,

p-cyclopentyl-N-[6-(2-hydroxyethoxy)-5-p-tolyl]benzenesulphonamide,

α,α,α-trifluoro-N-[6-(2-hydroxyethoxy)-5-p-tolyl-4-pyrimidinyl]-o-toluenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-p-tolyl-4-pyrimidinyl]-o-toluenesulphonamide,

p-chloro-N-[6-(2-hydroxyethoxy)-5-(1-naphthylmethyl)-4-pyrimidinyl]benzenesulphonamide,

N-6-(2-hydroxyethoxy)-5-(p-isopropylphenyl)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide,

p-cyclopentyl-N-[6-(2-hydroxyethoxy)-5-(p-isopropylphenyl)-4-pyrimidinyl]benzenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-(α,α,α-trifluoro-p-tolyl)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide,

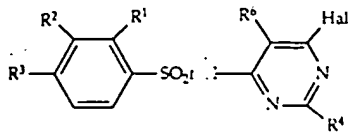
N-[5-(p-bromophenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl]-p-isopropylbenzenesulphonamide,

N-[6-(2-hydroxyethoxy)-5-(p-ethylphenyl)-4-pyrimidinyl]-p-isopropyl]benzenesulphonamide,

p-cyclopentyl-N-[6-(2-hydroxyethoxy)-5-(p-ethylphenyl)-4-pyrimidinyl]benzenesulphonamide.

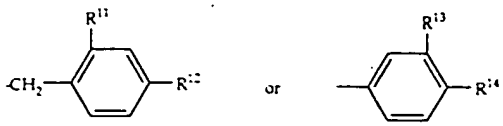
9. The compounds of any one of claims 3-8 for use as medicaments.

10. A process for the manufacture of the compounds of any one of claims 3-8, which process comprises reacting a compound of the formula



II

wherein R^1, R^2, R^3 and R^4 have the significance given in claim 1, Hal represents halogen and R^6 represents a residue



(c) or (d)

and R^{11}, R^{12}, R^{13} and R^{14} have the significance given in claims 2 and 6,

with a compound of the formula

$$MX(CH_2)_nYR^5 \qquad III$$

wherein X, Y, n and R^5 have the significance given in claim 1 and M represents an alkali metal,

and, if desired, modifying substituents present in the compound of formula I obtained and/or converting the compound of formula I obtained into a salt.

11. A pharmaceutical preparation containing a compound of any one of claims 3-8 and usual pharmaceutical adjuvants.

12. The compounds of any one of claims 3-8 whenever prepared by the process of claim 10 or by an obvious chemical equivalent thereof.

13. The novel compounds, preparations, processes and use as described hereinbefore.

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